

Human

PHYSIOLOGY

for medical students



DIGESTION
(GASTROINTESTINAL TRACT)

Magdi Sabry M.D.

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**HUMAN
PHYSIOLOGY
FOR MEDICAL STUDENTS**

DIGESTION (GASTROINTESTINAL TRACT)

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DEDICATED TO

MY TEACHERS THROUGHOUT MY LIFE, particularly the first 2 teachers, my late parents.

MY FAITHFUL LATE WIFE, the light that disappeared from life but is everlasting inside me.

MY SONS, SHERIF, AMR AND ESSAM, AND THEIR WIVES, their love gives me hope and interest in life and makes their happiness my chief goal.

MY GRANDCHILDREN, AHMED, NOURHAN & SAMA SHERIF, YASMIN & MOHAMMED AMR, AND AYA & ALY ESSAM, the beautiful young angels that have added a new kind of happiness to my life.

preface

With recent advances in the field of human physiology, it has become urgent to provide an up to date review on the subject.

This book is provided to help medical students in understanding modern human physiology. It presents the whole subject in a brief, comprehensive and up to date form.

Great effort was done to perfect such a vast subject in an easily understandable expression and in a such reasonable bulk. It includes as much simplified and clear illustrations as possible, and to maintain simplicity, they have been presented in a diagrammatic form, photographs were greatly excluded.

The major part of my gratitude should be given to all who taught me, and to my late wife and sons who, patiently, supported me during preparation of this book.

Any suggestions, remarks or criticism will be greatly welcomed, heartily appreciated and very much considered.

I hope this book will be a real help to undergraduate medical students as well as to postgraduates and candidates of higher degrees, in the field of human physiology.

MAGDI SABRY, 1989

Second edition : 1995

Third edition : 1999

Preface to the fourth edition

This new edition is original both in shape and contents. All chapters have been extensively revised and updated. More figures and illustrations were introduced, and recent data were added elsewhere specially about the gastrointestinal hormones and motility, and most subjects have been completely rewritten.

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THE DIGESTIVE SYSTEM

The digestive system provides the body with nutrients and water as well as various vitamins and minerals. It consists of the alimentary canal (= gastro-intestinal tract or GIT) and the glands that secrete digestive juices in it (= salivary glands, liver and pancreas). The GIT extends from the mouth to the anus, and it includes from above downwards : the buccal cavity, pharynx, esophagus, stomach, small intestine and large intestine (= colon) which ends by the rectum and anal canal (figure 1). The small intestine consists of 3 parts, which include from above downwards : the duodenum, jejunum and ileum.

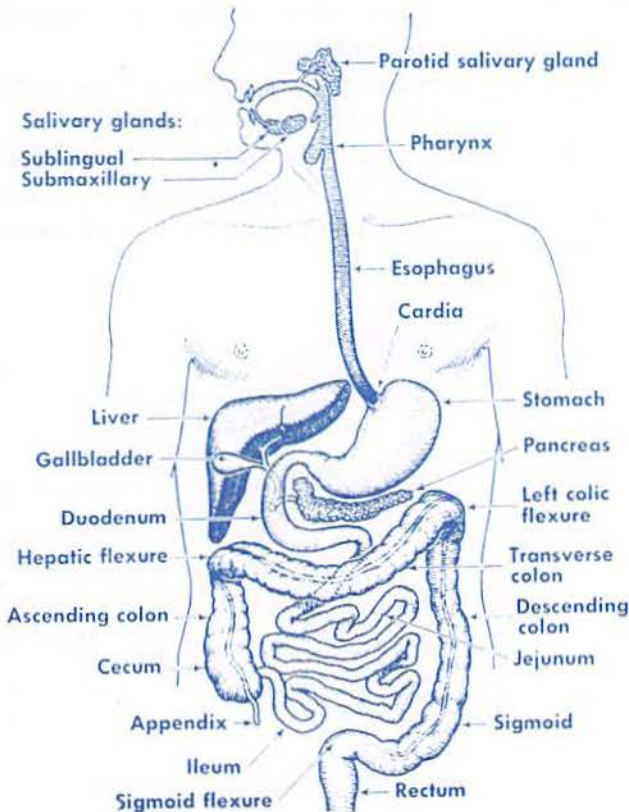


Figure 1 : The digestive system.

The various parts of the GIT are separated by special muscles called *sphincters* which control the passage of its contents from one part to the other e.g. the stomach is separated from the duodenum by the pyloric sphincter while the ileum is separated from the colon by the ileocolic (or ileocecal) sphincter (figure 3).

In living humans, the mean length of the duodenum is 25 cm while that of the jejunum & ileum is 260 cm and that of the colon 110 cm. However, after death the GIT relaxes and elongates. Thus, while the length of the small intestine during life averages 285 cm, it increases markedly in cadavers.

Functions of the GIT

- (1) **Digestion of food** : Dige'stion is the process of breakdown of proteins, fats and carbohydrates into simple particles that can easily be absorbed.
- (2) **Secretion of digestive juices** : These contain the various enzymes that are required for the process of food digestion.
- (3) **Absorption of the products of digestion** (as well as various vitamins, minerals and fluids) into the blood and lymph vessels.
- (4) **Excretion of the undigested and nonabsorbed substances in feces.**
- (5) **Motility** : This is essential for the processes of digestion, absorption and excretion through mixing and propulsion of the GIT contents.

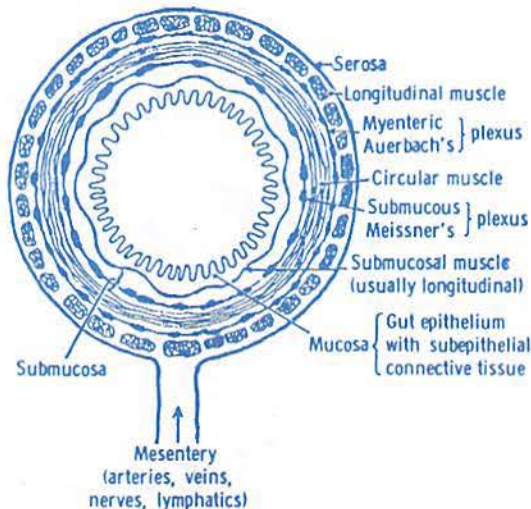


Figure 2 : Structure of the GIT wall.

Structure of the GIT wall

Generally, the GIT wall is composed of 4 layers, which are arranged as follows from *inside outwards* (figure 2) :

(1) **Mucosa (= mucous membrane)** : This is concerned with secretion of the digestive juices and certain hormones as well as absorption of the various nutrients. It contains blood capillaries and lymph vessels and a layer of smooth muscle called the *muscularis mucosae*.

(2) **Submucosa** : This is a dense connective tissue layer that contains larger blood and lymph vessels as well as a prominent nerve plexus called the *submucosal (or Meissner's) plexus*.

(3) **Musculosa (muscle coat)**: This consists of an outer longitudinal layer and an inner circular layer of smooth muscle with a well-developed nerve plexus in between called the *myenteric (or Auerbach's) plexus*.

(4) **Serosa** : This is a membrane that covers the GIT (except at the esophagus and distal rectum). It continues with the mesentery which contains the nerves and blood & lymph vessels that supply the GIT (figure 2).

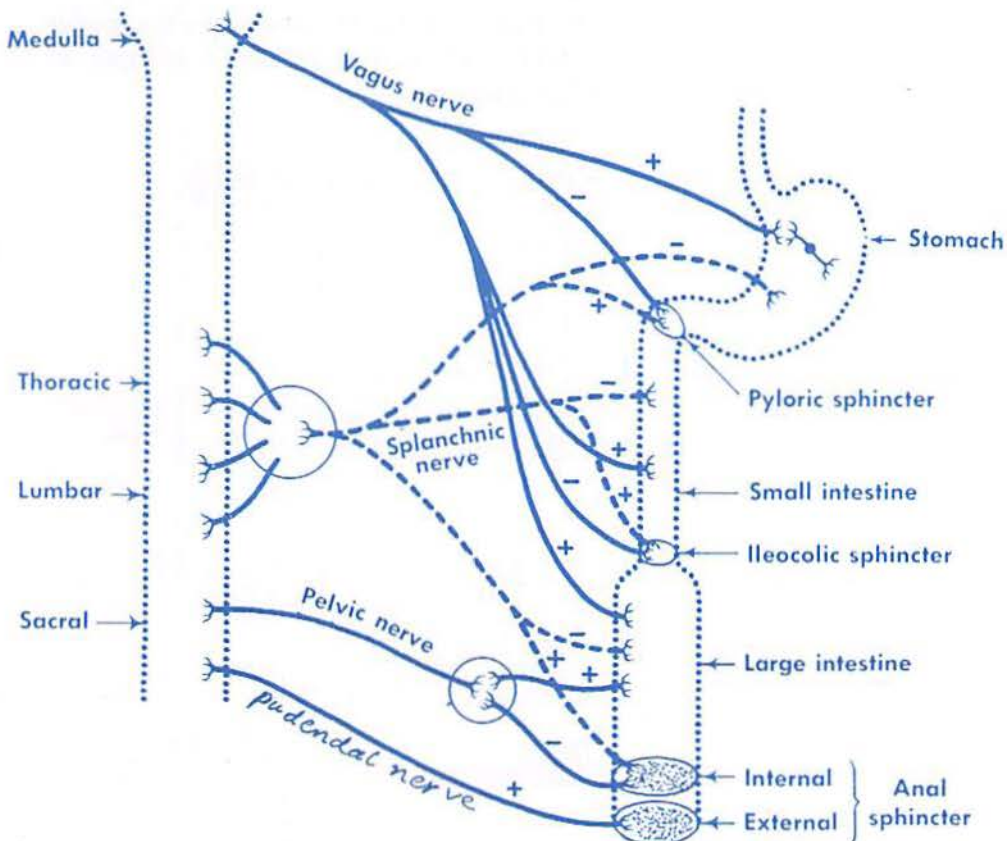


Figure 3 : Nerve supply of the GIT.

Innervation (nerve supply) of the GIT

The GIT receives nerve fibres from both the parasympathetic and sympathetic divisions of the autonomic nervous system as follows (figure 3) :

(1) **Parasympathetic fibres** : These are *cholinergic preganglionic fibres* that reach the GIT via the *vagi and pelvic nerves*, and they terminate at the neurons of the *intrinsic nerve plexuses (the myenteric and submucosal nerve plexuses)*. The vagi nerves supply the esophagus, stomach, small intestine and the upper part of the large intestine, while the pelvic nerves supply the lower part of the large intestine as well as the rectum and anal canal. Parasympathetic stimulation generally increases the secretory and motor activities of the GIT and causes relaxation of its sphincters.

(2) **Sympathetic fibres** : These are *noradrenergic postganglionic fibres* that arise from the prevertebral (= collateral) autonomic ganglia in the abdomen and reach the GIT via the *splanchnic nerves*. Most of these fibres terminate at the neurons of the intrinsic nerve plexuses while some innervate the blood vessels (producing V.C.) and some directly supply the smooth muscle. Sympathetic stimulation generally decreases the motor and secretory activities of the GIT, and causes contraction of both its sphincters as well as the muscularis mucosae.

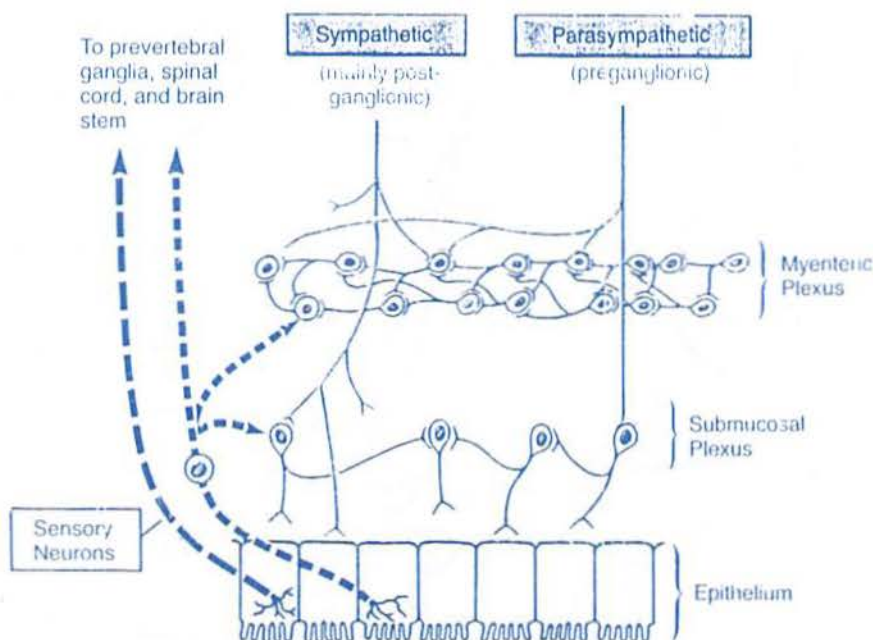


Figure 4 : The enteric nervous system .

The Enteric Nervous System (E.N.S.)

This consists of the *myenteric* (= *Auerbach's*) and the *submucosal* (= *Meissner's*) *nerve plexuses* (figure 4). Each of these plexuses is formed of a large number of neurons which are connected by interneurons (there are about 100 million neurons in both plexuses). Such system appears *at the lower 2/3 of the esophagus and extends to the distal part of the colon*, and most of the extrinsic autonomic nerves synapse with its neurons (however, the E.N.S. can function independent of these nerves). The parasympathetic nerve supply is generally stimulatory to the E.N.S. while the sympathetic nerve supply is inhibitory. *The Auerbach's plexus mainly controls the motor activity of the GIT while the Meissner's plexus mainly controls the intestinal secretions and the muscularis mucosae.*

The E.N.S. is probably a displaced part of the CNS that is concerned with regulation of gastrointestinal function, and it contains the following types of neurons :

- (1) **Motor neurons** : These innervate the smooth muscle.
- (2) **Secretory neurons** : These regulate both the endocrine and exocrine secretions of the mucosal cells.
- (3) **Sensory neurons** (specially in the submucosal plexus) : These respond to stretch and changes in tonicity as well as to several chemical stimuli

Many excitatory and inhibitory neurotransmitters are present in the E.N.S. including *acetylcholine, norepinephrine, serotonin, dopamine, ATP, GABA (gamma aminobutyric acid) and the gases NO and CO*, as well as *the peptides : VIP (vasoactive intestinal peptide), CCK (cholecystokinin), GRP (gastrin-releasing polypeptide), galanin, substance P, neuropeptide Y, somatostatin, neurotensin and certain endothelins and enkephalins.*

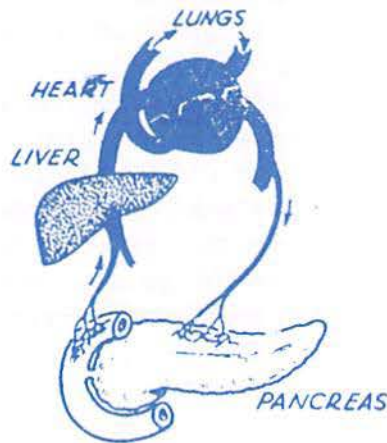


Figure 5 : Hormonal regulation of the GIT. In this case, the hormones are secreted from the duodenal mucosa and stimulate pancreatic secretion.

Regulation of gastrointestinal functions

The functions of the GIT are regulated by 2 main mechanisms :

(A) Nervous regulation

This occurs through the following reflexes :

(1) **Local axon (or local enteric) reflexes** : These are short reflexes that are confined to the E.N.S. (i.e. *all components of such reflexes are located in the GIT wall*) e.g. the *reflexes that lead to peristaltic movement and secretion of many gastrointestinal hormones*.

(2) **Ganglionic reflexes** : These reflexes start from receptors in the GIT to the *prevertebral sympathetic ganglia* then back to the GIT (i.e. these ganglia act as nerve centres in this case) e.g. the *enterogastric, gastrocolic and colonoileal reflexes*.

(3) **Central nervous reflexes** : These are long reflexes that start from receptors in the GIT to *the spinal cord or brain stem* then back to the GIT e.g. the *defecation reflex and the vagovagal reflexes* that lead to secretion of many digestive juices.

(B) Hormonal regulation

A group of polypeptide hormones are secreted by certain cells in the mucosa of the GIT (= enteroendocrine cells) and via the portal vein they reach the liver from which they are delivered to the systemic circulation. Such *gastrointestinal hormones are local hormones* i.e. they act locally at the GIT (controlling its motility and secretory activity) but at *other sites than those which released them* (figure 5).

Depending on structural similarity, the gastrointestinal hormones are divided into 2 main families :

(1) **Gastrin family** : This includes gastrin and cholecystokinin (CCK).

(2) **Secretin family** : This includes secretin, gastric inhibitory peptide (= GIP), vasoactive intestinal peptide (= VIP), glucagon and glicentin.

There are other hormonally-active polypeptides that are secreted by the GIT mucosa *but do not fall into these families* e.g. *motilin, guanylin, substance P, neurotensin, gastrin-releasing polypeptide* (= GRP = *bombesin in amphibia*) and *somatostatin* (see chapter 9).

MASTICATION, SALIVARY SECRETION AND DEGLUTITION

In the buccal cavity, *food mastication and salivary secretion take place* resulting in formation of a suitable bolus. This is followed by *deglutition (= swallowing)* which involves propulsion of the bolus into the pharynx then downward through the esophagus to the stomach.

MASTICATION (CHEWING)

Mastication is the process of breakdown of large food particles into small pieces. It involves the actions of the teeth and molars as well as the movements of the lips, tongue and mandible. Mandibular movements are performed by the *muscles of mastication* (= the masseter, temporalis and medial and lateral pterygoid muscles) which are supplied by the mandibular (motor) branch of the *trigeminal nerve* (= 5th cranial nerve). Such movements can occur voluntarily but the rhythmic opening and closing of the mouth during mastication is primarily the result of a *chewing reflex*, the centre of which is present in the brain stem.

Functions of mastication

- (1) It *helps swallowing* by mixing the food particles with saliva and formation of a bolus that can easily be swallowed.
- (2) It *helps digestion* by increasing the exposed surface area of food to the action of the digestive enzymes
- (3) It *reduces the mechanical damage* to the GIT mucosa.
- (4) It leads to *stimulation of the taste and smell receptors* (which is important for sensing the flavour of food).

SALIVARY SECRETION

Saliva is secreted by 3 pairs of salivary glands; the parotid (20 %), submandibular or submaxillary (70 %) and sublingual glands (5 %) as well as by the lingual (= Ebner's) glands present on the dorsum of the tongue and several small glands scattered in the mucous membrane of the buccal cavity (5 %). Each gland is formed of groups of acini, the secretion of which is carried by a duct which opens into the buccal cavity. The acini consist of 2 types of cells :

- (1) **Serous cells** : These are present in the parotid and submandibular glands and they secrete thin (watery) saliva rich in the enzyme ptyalin (an alpha amylase).

(2) **Mucous cells** : These are present in the sublingual and submandibular glands and they secrete thick (viscid) saliva rich in mucin (a glycoprotein that forms mucus when dissolved in water).

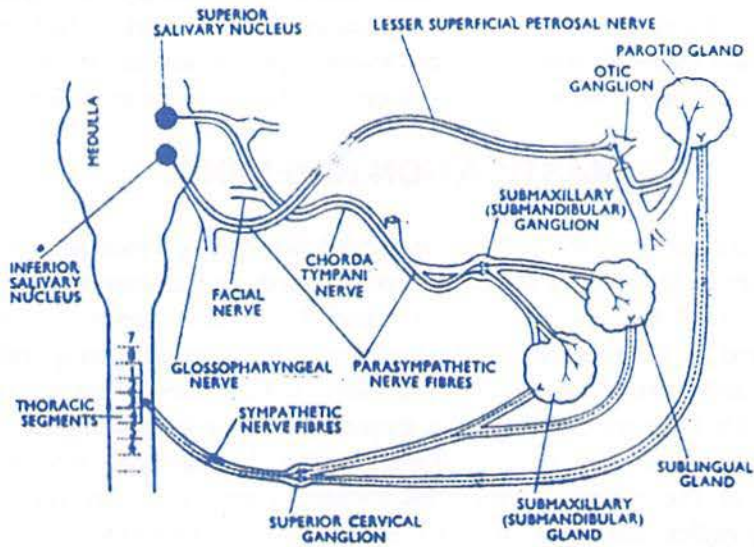


Figure 6 : Nerve supply of the salivary glands.

INNERVATION (NERVE SUPPLY) OF THE SALIVARY GLANDS

The salivary glands are supplied by *symp. & parasymp. nerves* (figure 6) :

(1) Sympathetic nerves

Preganglionic fibres arise from the lateral horn cells of the upper 2 thoracic segments of the spinal cord and relay in the superior cervical ganglion, from which noradrenergic postganglionic fibres arise and supply the salivary glands. Through acting on α_1 and β_2 receptors, sympathetic stimulation produces (a) **Trophic secretion** i.e. little secretion of viscous saliva rich in organic constituents (mucin and ptyalin) (b) **V.C.** in the salivary glands (c) **Contraction of the myoepithelial cells that surround the acini** (which facilitates expulsion of the secreted saliva).

(2) Parasympathetic nerves

The submandibular and sublingual glands are supplied by a branch from the facial nerve (= 7th cranial nerve) called the *chorda tympani*, which originates from the superior salivary nucleus in the lower pons and relays in the *submandibular* (= *submaxillary*) *ganglion* (from which postganglionic nerve fibres arise and supply these 2 glands). On the other hand, the parotid gland is supplied by a branch from the glossopharyngeal nerve (= 9th cranial nerve) called the *lesser superficial petrosal nerve*,

which originates from the inferior salivary nucleus in the medulla oblongata and relays in the **otic ganglion** (from which postganglionic nerve fibres arise and supply the parotid gland).

Parasympathetic stimulation produces **2 main effects** :

(a) **True secretion** i.e. profuse (large amount) secretion of watery saliva with a relatively low content of organic material. Such effect is produced by the parasympathetic neurotransmitter **acetylcholine**.

(b) **V.D.** in the salivary glands. Such effect is produced by locally-released **VIP** (which is a co-transmitter with acetylcholine).

Stimulation of the salivary nuclei also produces sympathetic effects because they also excite the lateral horn cells in the spinal cord.

MECHANISM OF SALIVARY SECRETION

Salivation *should occur rapidly* because food normally stays in the buccal cavity for a very short time. For this reason, it is normally **under nervous control only through conditioned and unconditioned reflexes**.

(1) Conditioned (psychic) reflexes

These are **acquired reflexes** that develop by **learning and training** and need an **intact cerebral cortex**. Seeing, smelling or even thinking of food stimulates salivation (specially if the subject is hungry).

Mechanism of the conditioned reflexes :

The sight of food excites the visual receptors in the eye (figure 7), from which impulses arise and are transported by afferent nerve fibres (in the optic nerve) to the visual centre (in the occipital lobe of the cerebral cortex). The latter, in turn, stimulates the salivary nuclei in the brain stem, from which impulses are transported by efferent parasympathetic and sympathetic nerve fibres to the salivary glands stimulating their secretion.

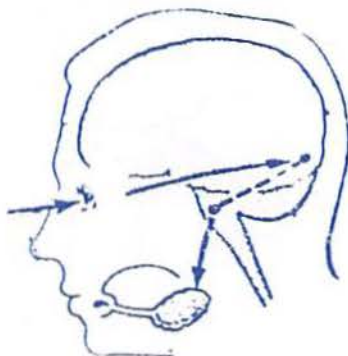


Figure 7 : Mechanism of salivary secretion by conditioned reflexes (in this case, seeing food leads to salivary secretion).

Pavlov's experiment

Pavlov (a Russian physiologist) **proved that conditioned reflexes are not inherent, but they are acquired by learning and training**. He showed

dogs a flash of light or made them hear the sound of an alarm clock just before eating, and such pairing process was repeated for several days. After this period, he found that only the light (or sound) was enough to produce salivation, as shown by dribbling of saliva from a fistula inserted into the parotid gland (figure 8) indicating that the animals have developed conditioned reflexes to these stimuli.

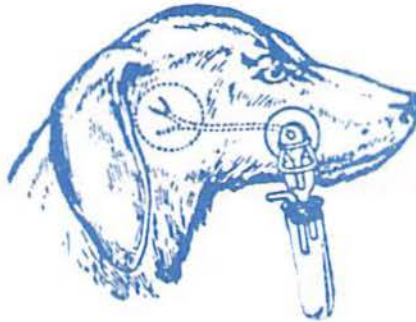


Figure 8 : A parotid fistula.

(2) Unconditioned reflexes

These are *inherent* (= *inborn*) *reflexes* that do not require learning or an intact cerebral cortex. The introduction of food in the buccal cavity (or mechanical stimulation e.g. by dental instruments) leads to reflex salivary secretion. This occurs due to stimulation of the *taste (and other) receptors in the buccal cavity*, from which impulses arise and are transported via afferent fibres in the 7th and 9th cranial nerves to the brain stem, where they stimulate the salivary nuclei resulting in salivary secretion (figure 9).

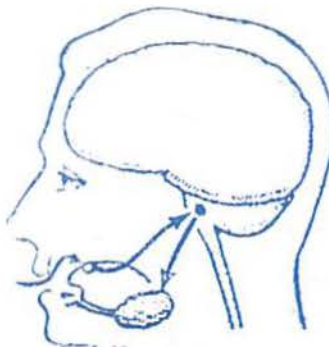


Figure 9 : Mechanism of salivary secretion by unconditioned reflexes.

The esophago-salivary and gastro-salivary reflexes

These are also *inherent unconditioned reflexes*. Irritation of the lower end of the esophagus, stomach or upper part of the small intestine (e.g. before vomiting) leads to reflex salivation. Such reflexes are initiated by nerve impulses that originate in the walls of the irritated viscera

and are transported via *afferent vagal nerve fibres* to the brain stem where they stimulate the salivary nuclei. They provide additional saliva which dilutes or neutralizes the irritant in the esophagus and sets up peristalsis that drives it downwards. In case of vomiting, the secreted saliva helps to buffer the acidic gastric contents.

FORMATION AND COMPOSITION OF SALIVA

The amount of saliva secreted daily is about **1.5 litres**, and its pH is about 7, but during active secretion it approaches 8 due to addition of HCO_3^- (see below). It is *hyposmotic* (hypotonic) relative to the plasma, and it contains about **99.5 % water and 0.5 % solids** which include :

(1) **Inorganic ions** e.g. Na^+ , K^+ , Cl^- and HCO_3^- (which act as buffers and activators) as well as Ca phosphate and bicarbonate.

(2) **Organic constituents** : These are mainly the digestive enzymes *ptyalin* and *lingual lipase* (the latter is secreted by Ebner's glands) and *mucin*. In addition, saliva also contains *IgA*, *lysozyme*, *lactoferrin* (*bacteriostatic*), *proline-rich proteins* (the latter protect the teeth enamel).

The formation of saliva is an **active secretory process**. Most of the inorganic ions are secreted by the acinar cells together with mucin and ptyalin. The initial secretion from the acini is isotonic. However, in the ducts, the salivary composition is modified by extracting Na^+ & Cl^- and adding K^+ & HCO_3^- (so it becomes alkaline). The duct walls are also relatively impermeable to water, so the saliva becomes hypotonic.

Evidences that salivary secretion is an active (vital) process

The following evidences prove that the formation of saliva is not a simple process of filtration or diffusion from the blood :

(1) The salivary glands can secrete saliva *against pressures in their ducts that are higher than the arterial blood pressure*.

(2) The O_2 consumption of the salivary glands *increases about 5 times during activity (i.e secretion)* compared with that at rest.

(3) The composition of saliva is *different from that of the plasma*.

(4) *After atropine injection, parasymp. stimulation does not lead to salivary secretion* although V.D. still occurs in the salivary glands due to release of VIP (page 9).

FUNCTIONS OF SALIVA

(1) **Digestive function** : The enzyme *ptyalin* (= *salivary alpha-amylase*) starts digestion of starch (specially cooked starch). It splits starch into smaller molecules i.e. oligosaccharides (the disaccharide maltose, the trisaccharide maltotriose, and alpha-limit dextrins). The optimum pH for its action is 6.7, and *it requires Cl^- as a coenzyme (activator)*. However, it plays a *minor role in starch digestion* because it is rapidly inhibited by the

potent gastric acidity. The *lingual lipase* enzyme starts lipid digestion (it acts on triglycerides forming fatty acids and glycerol).

(2) It keeps the buccal cavity moist, which helps articulation (i.e. *aiding speech*) by facilitating the movements of the lips and tongue.

(3) Its mucin content lubricates food, thus facilitating the process of *swallowing* (= *deglutition*).

(4) It serves as a *solvent* for the molecules that stimulate the taste receptors, thus *facilitating the taste sensation*.

(5) It keeps the *mouth and teeth clean*, and it contains an *anti-bacterial enzyme* (= lysozyme) as well as *IgA* (= immunoglobulin A). Therefore, deficient salivation (= *xerostomia*) predisposes to buccal inflammation (= *stomatitis*) and dental caries, and causes *dysphagia* (= difficult swallowing) and *dysphasia* (= difficult speech).

(6) The salivary *buffers* (bicarbonates and mucin) *keep the oral pH at about 7 and antagonize its change*. This is important since acidity increases calcium solubility leading to its loss from the enamel of the teeth. The salivary buffers also neutralize the gastric acidity & *relieve the heartburn* that results from regurgitation of the gastric juice into the esophagus.

(7) The saliva acts as a *dilution medium* for irritant substances.

(8) It helps *heat loss* (through evaporation), specially in panting animals e.g. dogs (refer to body temperature regulation in metabolism).

(9) Decreased salivation in cases of dehydration leads to the *sensation of thirst*, which drives the patient to drink. This helps to maintain a normal *water balance* in the body.

(10) It is an *excretory channel* for certain organic substances (e.g. urea) as well as some inorganic salts (e.g. salts of mercury, lead, iodine and fluorine). The latter protects the teeth enamel and prevents dental caries.

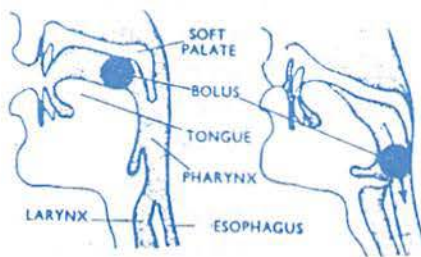


Figure 10 : The buccal and pharyngeal stages of deglutition. Notice closure of the mouth and elevation of the tongue, soft palate & larynx.

DEGLUTITION (SWALLOWING)

Deglutition is the act of transferring food from the buccal cavity to the stomach. It can be studied from *successive x-rays* taken while swallowing a barium sulphate solution (*barium meal*). The process is divided into 3

stages : (1) Buccal stage (2) Pharyngeal stage (3) Esophageal stage.

(1) BUCCAL STAGE

This is a *voluntary stage*. After mastication and formation of a suitable bolus, the tongue is voluntarily elevated against the hard palate (mainly by contraction of the *mylohyoid muscles*) so the bolus is propelled backwards into the pharynx. The *mouth must be closed* (so swallowing becomes difficult if the mouth is open e.g. while a dentist is working in the mouth).

(2) PHARYNGEAL STAGE

This is an *involuntary stage* because it occurs as a result of a reflex called the *swallowing reflex* that cannot be prevented once it starts.. As the bolus is pushed backwards, it stimulates certain receptors located at the pharyngeal opening specially in the tonsillar pillars (= *swallowing receptor areas*) and the resulting signals are transported via afferent nerve fibres in the 5th, 9th and 10th cranial nerves to a *swallowing (or deglutition) centre in the medulla oblongata*. From this centre, impulses are discharged via efferent nerve fibres in the 5th, 7th, 9th, 10th and 12th cranial nerves, leading to the following effects :

(A) PROTECTIVE REFLEXES

These reflexes *prevent food entrance into the nasal cavities and trachea and its regurge back into the buccal cavity*. They include :

(a) **Elevation of the soft palate** : This shuts off the posterior nasal openings, thus preventing food reflux into the nasal cavities (figure 10).

(b) **Elevation of the larynx against the epiglottis** : This closes the superior laryngeal orifice (= glottis), thus preventing food entrance into the trachea (figure 10).

(c) **Approximation of the vocal cords** : This also closes the glottis, but its role is *more important than that of the epiglottis*.

(d) **Temporary apnea** (stoppage of breathing) : The deglutition centre discharges inhibitory impulses to the respiratory centre leading to apnea for a few seconds, which also prevents food entrance into the trachea.

(e) **Approximation of the palato-pharyngeal folds** : This prevents entrance of large food particles into the pharynx, allowing only passage of food that has been properly masticated.

Since the swallowing reflex is initiated by contact of food with specific receptor areas in the throat (see above), if these areas are anesthetized (e.g. by painting them with cocaine) swallowing becomes impossible.

(B) PHARYNGEAL PERISTALSIS

Following the protective reflexes, the muscular wall of the pharynx contracts. A peristaltic wave begins in the superior part of the pharynx and extends rapidly downward over its middle and inferior parts, leading to push of the food bolus into the esophagus. This is helped by *relaxation of the pharyngo-esophageal (= upper esophageal) sphincter*, and the entire process takes place in less than 2 seconds.

(3) ESOPHAGEAL STAGE

This is also *an involuntary stage* in which a peristaltic movement is initiated in the upper part of the esophagus then it extends downwards along its wall, resulting in propulsion of the food bolus into the stomach.

Depending on the nature of muscle in the esophageal wall, the esophagus can be divided into 3 parts : *the upper 1/3 contains striated muscle only, the lower 1/3 contains smooth muscle only, while the middle 1/3 contains both types of muscle (but the smooth type is predominant).* There are 2 types of esophageal peristalsis :

(1) **Primary peristalsis** : This is a continuation of the peristaltic wave that begins in the pharynx.

(2) **Secondary peristalsis** : This occurs if the primary peristalsis fails to propel all food that has entered the esophagus. It *originates in the esophagus itself as a result of distention of its wall by food.*

The esophageal peristalsis travels at a rate 3-4 cm /second (traversing the esophagus in about 8-10 seconds). However, in the upright position, food moves faster *by the effect of gravity*, so it can be transmitted to the lower end of the esophagus in only 5-8 seconds.

NERVOUS CONTROL OF ESOPHAGEAL PERISTALSIS

The striated muscle in the upper 1/3 is *directly controlled by the vagi nerves* and its movement is *rapid*, while the smooth muscle in the lower 2/3 is *indirectly controlled by the vagi* (through their connections with the **enteric nervous system**, which first appears in this part) and its movement is *slow*.

Both types of esophageal peristalsis require *integrity of the vagi nerves*. The primary type is produced by efferent vagal nerve fibres while the secondary type is produced through a *vago-vagal reflex*. Secondary peristalsis *in the lower part* of the esophagus can also be initiated by **local enteric reflexes**. Therefore, *bilateral vagotomy abolishes both primary and secondary peristalsis in the upper part of the esophagus while secondary peristalsis returns within a few days in the lower part.*

The following table summarizes the main differences between the upper and lower thirds of the esophagus :

	UPPER THIRD	LOWER THIRD
Musculature	Striated	Smooth
Nerve Supply	Vagus nerve only (direct)	Vagus nerve + E.N.S.
Movement	Rapid	Slow
Effect of bilateral vagotomy	Complete paralysis	Secondary peristalsis persists

THE ESOPHAGEAL SPHINCTERS

(1) **Upper esophageal sphincter (UES)** : This is the upper 3-4 cm of the esophagus and is also called the *pharyngo-esophageal sphincter*. The resting tension in this sphincter is normally high. This *prevents aero-phagia* (= excessive air entrance into the stomach). During swallowing, it relaxes temporarily to allow the bolus to be forced into the esophagus by effect of the pharyngeal peristalsis. It then contracts again, preventing food reflux (regurgitation) from the esophagus back into the pharynx.

(2) **Lower esophageal sphincter (LES)** : This is the lower 3 cm of the esophagus and is also called the *gastroesophageal or cardiac sphincter*. It is a functional sphincter that is *normally tonically contracted* between meals to prevent reflux of the gastric contents into the esophagus. However, it temporarily relaxes during swallowing, but it soon contracts again after the bolus passes into the stomach. Its *relaxation is mediated by VIP and NO* (which are released by the myenteric plexus at the lower end of the esophagus).

If the tone of the LES is decreased, it becomes incompetent and the gastric contents regurgitate into the esophagus (= *gastroesophageal reflux disease*) causing *heartburn* (and in long standing cases, it may lead to *esophagitis, esophageal ulceration or esophageal stricture due to scarring*).

SWALLOWING DISORDERS

(A) DYSPHAGIA

This is *difficult swallowing*. Its common causes are the following :

- (1) Lesions of the 9th or 10th cranial nerves (e.g. due to diphtheria).
- (2) Damage of the deglutition centre (e.g. in poliomyelitis).
- (3) Malfunction of the swallowing muscles (e.g. in myasthenia gravis).
- (4) Esophageal strictures (= narrowing) e.g. due to cancer or scarring.

(B) ACHALASIA (= CARDIOSPASM)

This is a condition characterized by *increased resting tension in the LES*. As a result, food transfer from the esophagus to the stomach is delayed or blocked, so food accumulates in the esophagus and, accordingly, it becomes severely dilated. The condition is due to *deficiency of NO and VIP* as a result of defective development of the myenteric plexus in the lower part of the esophagus. It can be treated by either (a) *Pneumatic dilatation of the LES* or (b) Incision of the esophageal muscle (= *myotomy*).

CHAPTER 3

THE STOMACH

FUNCTIONAL ANATOMY

The human stomach is formed of 3 main parts (figure 11) : *fundus*, *body* and *antrum*. The latter continues as a short *pyloric canal* that ends by the *pylorus* (the opening of the stomach into the duodenum) which is surrounded by the *pyloric sphincter*. The constriction between the body and antrum at the lesser curvature is called the *incisura angularis*. The opening of the esophagus into the stomach is called the *cardia*, and is controlled by the *lower esophageal (= cardiac) sphincter*.

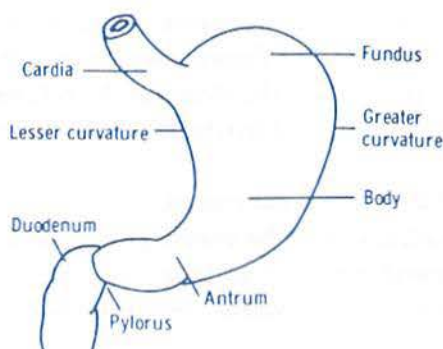


Figure 11 : The human stomach.

THE GASTRIC MUCOUS MEMBRANE

This contains *simple tubular glands* which open at the mucosal surface at special *gastric pits* (figure 12). It is thrown out into large folds called *rugae* by contraction of the muscularis mucosae. The glands in the cardiac region and pyloric canal contain mainly mucous cells while those in the fundus and body contain the following cells :

- (1) **Oxyntic (= parietal) cells** : These secrete *HCl* and the *intrinsic factor* (which is essential for absorption of vitamin B₁₂). They also secrete a polypeptide hormone called **GHRELIN** which increases food intake and stimulates secretion of the growth hormone (refer to endocrine glands).
- (2) **Peptic (= chief) cells** : These secrete mainly *proteolytic enzymes (pepsinogens)* as well as other enzymes (see below).
- (3) **Mucous cells** : These secrete *mucus*, and are present in the neck of the glands as well as in the surface epithelium.

The antral glands (in the pyloric antrum) also contain the 3 types of cells, but they are poor in the oxyntic and peptic cells and, in addition, they contain the *G cells that secrete the gastrin hormone* (see below).

- (4) **Enterochromaffin like cells** : These secrete histamine (page 24).

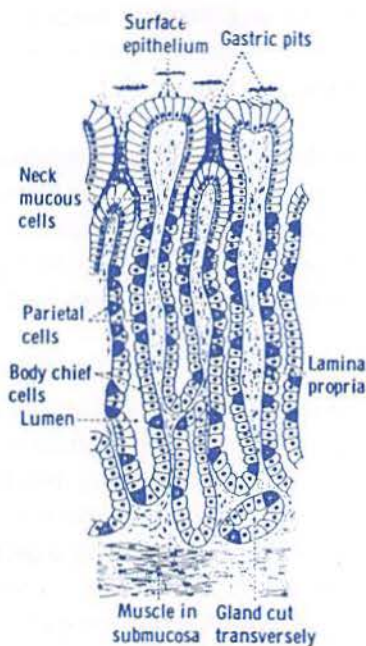


Figure 12 : The gastric mucosa.

INNERVATION (NERVE SUPPLY) OF THE STOMACH

The stomach receives sympathetic and parasympathetic nerves :

(A) Sympathetic supply : This is derived from the celiac ganglion via the *greater splanchnic nerves*, and its stimulation leads to :

- (1) Relaxation of the stomach wall and contraction of the pyloric sphincter (resulting in delayed gastric emptying).
- (2) Stimulation of mucus secretion from the pyloric mucosa.
- (3) V.C. of the gastric blood vessels.

(B) Parasympathetic supply : This is derived from the *vagi nerves*, and its stimulation leads to :

- (1) Contraction of the stomach wall and relaxation of the pyloric sphincter (resulting in accelerated gastric emptying).
- (2) A secretion rich in HCl and pepsinogens.
- (3) V.D. of the gastric blood vessels.

Both symp.and parasymp.nerves also contain afferent fibres of the *long reflexes from the stomach* that control its motility & secretion (see below).

MECHANISM OF GASTRIC SECRETION

Gastric juice secretion passes in 3 phases : *cephalic, gastric and intestinal phases*.

I. Cephalic (nervous or psychic) phase

This phase occurs *before food reaches the stomach* (aiming at

preparing it to receive the coming meal). It takes place by **conditioned and unconditioned reflexes** which stimulate gastric secretion through impulses discharged in the *vagi nerves*.

(1) **Conditioned reflexes** : These are *acquired reflexes* that develop by learning and training and need an intact cerebral cortex. Seeing, smelling or thinking of food, lead to gastric secretion. Its mechanism is similar to that described in salivary secretion (page 9) but the impulses to the stomach are discharged from the vagus nucleus in the medulla oblongata.

(2) **Unconditioned reflexes** : These are *inherent (inborn) reflexes* that do not require learning or an intact cortex. Food introduction in the buccal cavity leads to gastric secretion by stimulating the taste and other sensory receptors (from which impulses are discharged to the medulla where they stimulate the vagus nucleus resulting in gastric secretion). These reflexes are proved by the *sham feeding experiment* (see below).

The vagal preganglionic nerve fibres terminate at the intrinsic nerve plexuses, the axons of which stimulate (a) The oxyntic and peptic cells by releasing acetylcholine (b) The gastrin-secreting cells (G cells) by releasing GRP (gastrin releasing polypeptide) and the secreted gastrin also stimulates the oxyntic and peptic cells. Therefore, vagal stimulation produces a gastric juice rich in HCl and pepsinogens due to stimulation of the oxyntic and peptic cells **both directly (by cholinergic fibres) and indirectly (by stimulating secretion of the gastrin hormone)**.

The volume of juice secreted in this phase is generally little (about 20 % of the total volume of the gastric juice), and is basically determined by the state of appetite as well as by many psychic factors (so it is called the *appetite or psychic juice*).

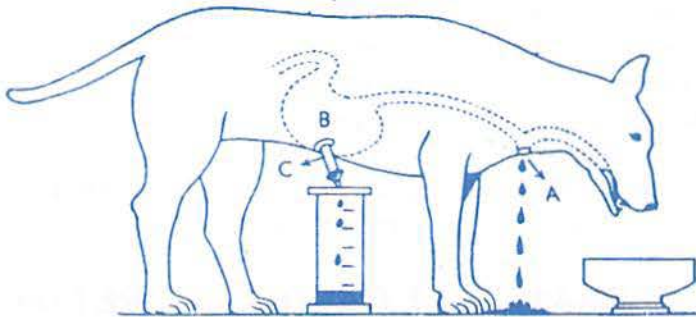


Figure 13 : The sham feeding experiment. A = opening in the neck. B = stomach. C = gastric fistula.

The sham feeding experiment

This is an experiment that demonstrates the role of the *unconditioned reflexes in the control of gastric secretion*. The esophagus of a dog is exposed and divided in the neck and the 2 cut ends are brought to the surface. At the same time, a gastric fistula is inserted (figure 13). In this way, any swallowed food escapes out through the opening in the neck and will not reach the stomach i.e. it is a *sham (= false) feeding*. Although no food reaches the stomach, yet when the animal eats, secretion of the gastric juice still occurs (as shown by its dribbling from the gastric fistula).

2. Gastric phase

This phase occurs *when food enters the stomach*. It constitutes the *main mechanism of gastric secretion* because it continues for about 3 hours and produces about 70 % of the total volume of the gastric juice. It occurs by *2 main mechanisms* :

(1) **Nervous mechanism** : This includes :

(a) *Local enteric(= short or local axon) reflexes* : Mechanical distention of the fundus and body of the stomach as well as chemical stimulation of the gastric mucosa by the products of digestion (particularly polypeptides) initiate local reflexes (involving mainly the submucosal nerve plexus) that result in gastric secretion.

(b) *Vago-vagal (= long) reflexes* : Mechanical distention and chemical stimulation of the gastric mucosa also initiate impulses that are transported via afferent vagal nerve fibres to the vagus nucleus in the medulla oblongata which in turn, discharges impulses via efferent vagal nerve fibres to the stomach leading to gastric secretion.

(2) Hormonal mechanism

This is the *main mechanism of gastric secretion*. Mechanical distension of the *pyloric antrum* or chemical stimulation of its mucosa result in secretion of the *gastrin hormone* from certain cells called *G cells* (= gastrin-secreting cells). The release of gastrin occurs *mainly by local enteric reflexes*, but vago-vagal reflexes also contribute in which the efferent vagal nerve fibres release GRP (gastrin-releasing polypeptide). Gastrin is transported by the bloodstream to the fundus and body of the stomach where it stimulates gastric secretion (figure 14).

3. Intestinal phase

The amino acids present in *chyme* (= *product of gastric digestion*) stimulate secretion of gastrin (= previously called *intestinal gastrin*) from the duodenal mucosa which produces little secretion of the gastric juice. However, the *intestinal influences on gastric activities are mostly inhibitory rather than excitatory*. The intestinal factors that inhibit gastric

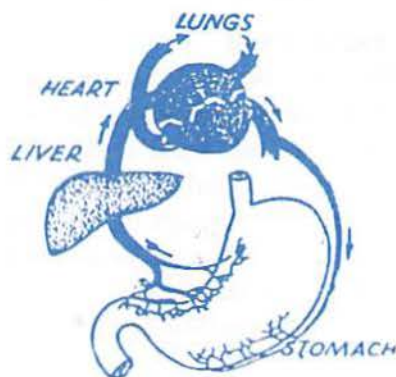


Figure 14 : Hormonal control of gastric secretion (role of gastrin).

secretion are (1) **Mechanical** (distention of the duodenum) (2) **Chemical** (presence of excess acid, fat and carbohydrate as well as irritant substances and hypertonic fluids in the duodenum).

Both factors inhibit gastric secretion through the **enterogastric reflex** (see below). In addition, the chemical factors stimulate secretion of **certain hormones from the duodenal mucosa that inhibit gastric secretion**. These hormones include **peptide YY (the most potent), CCK, secretin, VIP, somatostatin and GIP (= Gastric inhibitory polypeptide, or previously enterogastrone)**.

The enterogastric reflex

This is reflex inhibition of gastric secretion and motility in response to both duodenal distention as well as presence of certain chemical factors in the duodenum (see above). Such inhibition of gastric activities occurs by **3 ways** (a) A local enteric (short) reflex (b) A vago-vagal (long) reflex (c) A prevertebral ganglionic reflex, which is the main mechanism (page 6).

FACTORS THAT AFFECT GASTRIC SECRETION

(A) Factors that stimulate gastric secretion

- (1) Food ingestion, specially if associated with increased appetite (through conditioned and unconditioned reflexes).
- (2) Food entry into the stomach (mainly through liberation of the gastrin hormone) as well as taking alcohol or caffeine (which directly stimulate the gastric mucosa).
- (3) Certain emotions e.g. anger and anxiety (through impulses from the hypothalamus that stimulate the vagus nucleus in the medulla).
- (4) Hypoglycemia (through stimulating the feeding centre in the hypothalamus which in turn stimulates the vagus nucleus).
- (5) I.V. injection of certain amino acids (e.g. glycine and alanine).

(B) Factors that inhibit gastric secretion

- (1) Reduction of the pH in the pyloric antrum below 2, which inhibits release of the gastrin hormone (see below).
- (2) Duodenal distention as well as presence of excess acid, fat, irritants or hypertonic fluids in the duodenum (through the enterogastric reflex and release of inhibitory hormones (see above).
- (3) Certain emotions e.g. fear and depression (through impulses from the hypothalamus that inhibit the vagus nucleus).

THE GASTRIC JUICE

The gastric glands secrete about **2.5 litres of gastric juice daily** which is highly acidic (pH 1-2) because it is **rich in HCl**. Its constituents are :

- (1) **Water** : This forms most of the volume of the gastric juice.
- (2) **Inorganic ions** : These include both cations (mainly Na^+ , K^+ , Mg^{++} and H^+) and anions (mainly Cl^- , HPO_4^- and SO_4^{--}).
- (3) **Enzymes** : These are mainly **2 pepsinogens** (the precursors of pepsins), as well as other enzymes e.g. **gelatinase** (which liquefies gelatin) and **gastric lipase** (which hydrolyzes triglycerides into fatty acids and glycerol). **Rennin (= chymosin)** is a milk-coagulating enzyme that is present in the stomachs of young animals but is absent in man.
- (4) **Intrinsic factor** : This is formed by the oxyntic cells and is essential for the absorption of vitamin B_{12} in the lower ileum.
- (5) **Mucus** : This is 2 types :
 - (a) **Thin mucus** : This is the main secretion of the cardiac, antral and pyloric glands, and is also secreted by the neck cells of the gastric glands in the body and fundus (figure 12). It helps to lubricate food movement and to protect the stomach wall from digestion by the gastric enzymes.
 - (b) **Thick mucus** : This is viscid mucus that is secreted by the **surface epithelium of the gastric mucosa (which also secretes HCO_3^-)**. Together with the mucus secreted by the neck cells of the gastric glands, it forms a flexible gel layer (1- 1.5 mm thick) that coats the whole gastric mucosa, providing a major shell of protection for the stomach wall and also contributing to lubrication of food transport.

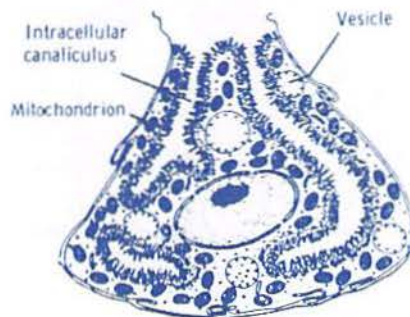


Figure 15 : The oxyntic (= parietal) cell.

Mechanisms of protection of the gastric mucosa

The gastric mucosa is protected from damage by HCl and auto-digestion by pepsins through the following mechanisms :

(1) The mucosal-cell membrane *naturally resists digestion* and the tight junctions between its cells prevent diffusion of HCl.

(2) The mucus gel layer together with the HCO_3^- secreted by the surface mucosal cells (see above), constitute a *mucosal barrier* that protects the gastric mucosa against damage by gastric HCl (through reducing the pH from 1-2 at the luminal side to 6-7 at the surface of the epithelial cells).

(3) The gastric *prostaglandins* help protection of the gastric mucosa because they *stimulate mucus and HCO_3^- secretion and inhibit acid secretion* (see below).

(4) The oxyntic cells are protected from HCl by forming that acid in *intracellular canaliculi* then secreting it in the gastric lumen (figure 15).

(5) The gastric mucosa contains certain peptides called *trefoil peptides* which are acid-resistant.

(6) There are several mechanisms that *decrease gastric acidity* (page 24) together with *continuous regeneration of the gastric mucosa*.

Secretion and actions of pepsinogens

There are 2 types of *pepsinogens* in the peptic (= chief) cells of the gastric mucosa. In these cells, they are present as *zymogen granules* which are secreted by *exocytosis*. The release of pepsinogens is stimulated by the *secretaeoeues* that stimulate acid secretion (*gastrin, histamine and acetylcholine*). They are inactive, and they become *activated to pepsins by HCl*. In addition, the formed pepsins further activate pepsinogens (= *autoactivation*). Pepsins are *proteolytic enzymes* which start protein digestion. They are *endopeptidases* that breakdown protein molecules into peptones, proteoses and polypeptides, and the optimum pH for their activity is 1.6 - 3.2.

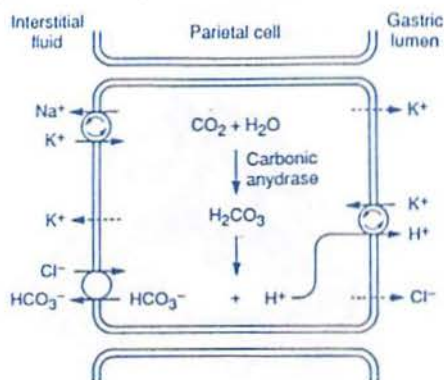


Figure 16 : Mechanism of HCl formation in the oxyntic (= parietal) cells.

THE GASTRIC HYDROCHLORIC ACID (HCl)

Mechanism of HCl formation

The steps of formation of gastric HCl are as follows (figure 16) :

(1) CO_2 combines with H_2O forming H_2CO_3 by activity of *the carbonic anhydrase enzyme* (which is abundant in the parietal cells). The formed H_2CO_3 then dissociates into H^+ and HCO_3^- .

(2) H^+ is pumped into the lumens of the canaliculi in exchange for K^+ by activity of H^+-K^+ ATPase, while HCO_3^- is extruded into the interstitial fluid in exchange for Cl^- (*by an antiporter*).

(3) Cl^- then diffuses into the canaliculi (where it combines with H^+ forming HCl which enters the gastric lumen).

****** Na^+-K^+ ATPase keeps the intracellular Na^+ concentration low by pumping Na^+ to the interstitial fluid in exchange for K^+ (figure 16). Thus the intracellular K^+ increases due to its exchange for both H^+ and Na^+ . However, it then diffuses into both the interstitial fluid (helping further Na^+ pump) and gastric lumen (helping further H^+ pump).

Postprandial alkaline tide : When gastric secretion increases after a meal, excess HCO_3^- is added to the blood by the parietal cells, *so the pH of the blood is increased and the urine becomes alkaline*. This effect is called the *postprandial alkaline tide*.

Control of HCl secretion

(A) **Inhibitory factors** : HCl secretion is inhibited by :

- (1) The hormones that inhibit gastric secretion (page 20).
- (2) The enterogastric reflex (page 20).
- (3) Prostaglandin E_2 (PGE_2) : This *antagonizes the effect of histamine* by decreasing the intracellular cyclic AMP via G_i protein (inhibitory G protein) (figure 17).

(B) **Stimulatory factors** : These are called *secretagogues*, and they include mainly *acetylcholine, histamine and gastrin* :

(1) **Acetylcholine** : This is released by postganglionic parasympathetic cholinergic nerve endings. It acts on *M_3 muscarinic receptors* in the parietal cell membranes leading to increase of the intracellular Ca^{++} which acts via protein kinases to increase the transport of H^+ into the gastric lumen by H^+-K^+ ATPase (figure 17).

(2) **Gastrin** : This hormone reaches the stomach via the bloodstream. It acts on *special gastrin receptors* in the parietal cell membranes leading to increase of the intracellular Ca^{++} , which increases H^+ secretion like acetylcholine (figure 17). In addition, *gastrin stimulates histamine secretion by the enterochromaffin like cells* (and this is probably the main mechanism by which gastrin stimulates H^+ secretion).

(3) **Histamine** : This is continuously secreted in small amounts by *the*

enterochromaffin like cells, and its release is increased by gastrin (see above). It acts on special receptors in the parietal cell membranes called *H₂ receptors* resulting in increase of the intracellular cyclic AMP via G_s protein (stimulatory G protein) which acts via protein kinases to increase the transport of H⁺ into the gastric lumen by H⁺-K⁺ ATPase (figure 17). Such action is inhibited by prostaglandin E₂ (see above).

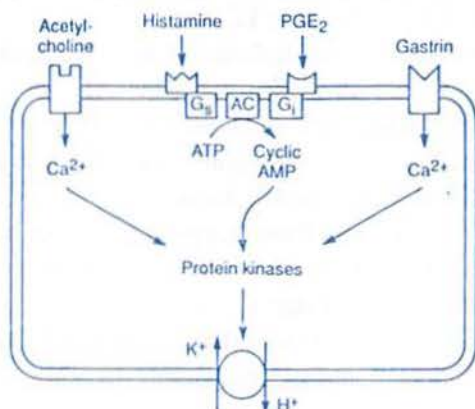


Figure 17 : The effects of prostaglandin E₂ and the various secretagogues on H⁺ secretion by the parietal cells, and the mechanisms of their actions (AC=Adenyl Cyclase enzyme, G = G protein).

Relation between HCl and gastrin secretion

There is a *negative feedback relation* between the amount of the secreted HCl and the rate of secretion of the gastrin hormone. Thus, an increase in HCl secretion inhibits gastrin secretion (which decreases HCl secretion) and vice versa (page 62). This is an important *autoregulatory mechanism for HCl secretion* because it protects the gastric mucosa from the damage that would occur if this acid is secreted in excessive amounts.

Mechanisms of decreasing excessive gastric acidity

- (1) Inhibition of release of gastrin by negative feedback (see above).
- (2) Increased secretion of mucus rich in HCO₃⁻ which neutralizes HCl.
- (3) When excessive acid enters the duodenum, it initiates the enterogastric reflex and stimulates secretion of hormones that inhibit gastric secretion (page 20).

Of more importance, is the **reduction of duodenal acidity** (since the duodenal mucosa is much more delicate than the gastric mucosa and develops ulcers more easily). *Excessive duodenal acidity is decreased by the following defensive mechanisms* :

- (1) Initiation of the enterogastric reflex and release of the inhibitory hormones (see above). These effects delay gastric emptying and reduce gastric HCl secretion (so the amount entering the duodenum is decreased). In addition, *secretin stimulates pancreatic & bile secretion* (these are rich in HCO₃⁻, which neutralize HCl in the duodenum and inactivate pepsin).

- (2) Increased mucus secretion in the duodenum (by Brunner's glands).
- (3) Regurgitation of excess acid back into the stomach.

FUNCTIONS OF HCl

- (1) It *activates pepsinogens into pepsins* (which start protein digestion) and provides an optimum pH for their action.
- (2) It sterilizes the stomach by *killing most ingested bacteria*.
- (3) It *stimulates bile flow and pancreatic secretion* (by stimulating release of the CCK and secretin hormones from the duodenal mucosa).
- (4) It causes *milk curdling*, which helps milk digestion (by keeping it in the stomach for a long time). This effect is produced by *rennin* in animals.
- (5) It helps absorption of *iron* [by converting ferric (Fe^{+++}) to ferrous (Fe^{++}) ions] and *calcium* (by preventing precipitation of calcium salts).
- (6) It *regulates gastric emptying* (with other factors) Entry of acid chyme in the duodenum delays gastric emptying through the enterogastric reflex and release of the gastric inhibitory hormones (page 20).

PEPTIC ULCER

This is erosion of an area in the mucosa of the stomach, duodenum or esophagus due to autodigestion by the gastric juice. It occurs as a result of *an imbalance between the rate of gastric secretion and the degree of mucosal protection* against autodigestion due to one of the following causes :

(A) **Excessive gastric secretion** due to either (1) Hereditary factors (2) Prolonged stress, depression or anxiety (3) Increased gastrin secretion from certain tumours called *gastrinomas* (= *Zollinger-Ellison syndrome*).

(B) **Excessive exposure of the mucosa to the gastric juice** : This is the main cause of (1) Esophageal ulcers (due to frequent *gastroesophageal reflux* of the gastric juice) (2) Duodenal ulcers (due to *deficiency of the defensive mechanisms that decrease duodenal acidity*).

(C) **Disruption (breakdown) of the mucosal barrier** : This is the main cause of gastric ulcers, and it may occur due to either :

- (1) Decreased mucus secretion (or secretion of an abnormal mucus).
- (2) Excessive intake of *gastric irritants* (e.g. alcohol, vinegar and spices).
- (3) Excessive intake of *aspirin*. This irritates the gastric mucosa and *inhibits synthesis of prostaglandins*, which normally decrease HCl secretion by antagonizing the action of histamine (page 23)
- (4) Infection of the gastric mucosa with certain types of bacteria (specially *helicobacter pylori*).
- (5) Excessive *smoking* (due to increased nervous stimulation of gastric secretion) and *alcohol* (which breaks down the mucosal barrier).

Physiology of treatment of peptic ulcer

On physiological basis, peptic ulcer can be treated by the following drugs :

- (1) Sedatives (which help to relieve depression, anxiety and stress).
- (2) H_2 receptor blockers which prevent the action of histamine (e.g. cimetidine, ranitidine and famotidine).

- (3) Prostaglandin agonists (e.g. *misoprostol*).
- (4) H^+-K^+ ATPase blockers (e.g. *omeprazole*).
- (5) Drugs that increase the mucosal resistance to acid by forming adherent protein complexes at the sites of ulcers (e.g. *sucralfate*).
- (6) Antacid drugs (commonly *aluminium or magnesium hydroxide*).

SUMMARY OF THE FUNCTIONS OF THE STOMACH

- (1) Storage of food.
- (2) Mixing food with the gastric juice (forming the partially-digested, almost *isotonic acid chyme*).
- (3) Emptying of the chyme into the duodenum at a *slow and steady (= piecemeal) rate* that is optimal for intestinal digestion and absorption.
- (4) Killing of bacteria (*sterilization function*) by HCl, which exerts other functions (page 25).
- (5) Digestion of fats and proteins (*by the gastric lipase and pepsins*).
- (6) Absorption of some substances e.g. *water and alcohol*.
- (7) *Red blood cell formation* by secreting HCl (which helps iron absorption) and the *intrinsic factor* (which is essential for vitamin B₁₂ absorption)
- (8) Initiation of reflexes that control gastric functions as well as other GIT functions e.g. *the gastroileal, gastrocolic and gastrosalivary reflexes*.

******: Atrophy of the gastric mucosa is called **achylia gastrica**. It is characterized by (1) *Pernicious anaemia* due to lack of the intrinsic factor (2) *Weakly-developed bones* due to lack of HCl (which helps calcium absorption) (3) *Liability to gastritis* due to absence of the bactericidal effect of HCl. However, *digestion proceeds almost normally* because digestion is normally completed by the intestinal and pancreatic enzymes.

GASTRIC MOTILITY

There are continuous mild contractions in the fundus and body called the *tonus rhythm* and on taking food, the stomach relaxes (= *receptive relaxation*). This is followed by *peristalsis* that mixes food with the gastric juice and then empties the gastric contents into the duodenum. If the stomach is empty for a long time, *hunger contractions* appear.

(1) RECEPTIVE RELAXATION

This is a *vagally-mediated reflex* that is triggered by movements of the pharynx and esophagus. Such relaxation is associated with *only a little increase in the intragastric pressure due to*:

(a) The gastric wall has the property of *plasticity* (i.e. it yields with persistent stretch leading to a little increase in tension).

(b) **Law of Laplace**: This law states that the distending pressure (P) in a hollow viscus equals the tension in its wall (T) divided by its radius (r) i.e. $P = T/r$. In the stomach, since food entry increases its radius with a little increase in tension, the intragastric pressure will be kept at a low level.

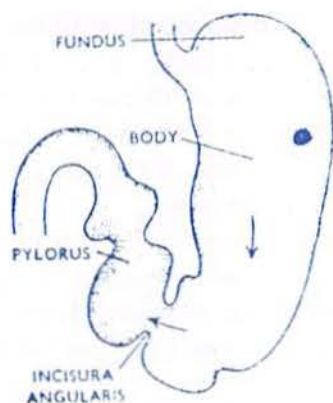


Figure 18 : Gastric peristalsis. The dark spot indicates the site of the pacemaker zone of BER.

(2) GASTRIC PERISTALSIS

This occurs at a rate of 3-4 /minute and is coordinated by the *basic electric rhythm (BER)* of the stomach (see below). The peristaltic waves start at the middle of the stomach and proceed towards the antrum (figure 18), where they become much stronger = *antral systole or pyloric pump*) then they continue in the pyloric canal. Such waves result in *grinding and propulsion of the gastric contents into the duodenum* through the pylorus. Normally, no duodenal regurgitation occurs because the pyloric contraction persists slightly longer than that of the duodenum.

The gastric basic electric rhythm (BER)

This is *spontaneous fluctuations in the membrane potential* of the gastric muscle cells that occur every about 15 seconds. It is initiated by certain pacemaker cells located at *a special zone in the greater curvature of the stomach* (figure 18). Spike potentials superimpose on the BER and such potentials increase the gastric muscle tone. On the other hand, the BER itself acts only as a *pacemaker for antral peristalsis* i.e. it only determines its rhythm but does not start muscle contraction (see page 51).

(3) HUNGER CONTRACTIONS

These are strong rhythmic peristaltic contractions that occur in the body of the stomach *when it is empty for several hours*. They may fuse together causing a tetanic contraction that lasts 2-3 minutes. The more intense contractions can be felt and may be mildly painful (= *hunger pains or hunger pangs*). Such pains usually appear 12-24 hours after the last ingestion of food and in case of starvation, they reach peak in 3 - 4 days then gradually weaken in the succeeding days.

Causes of hunger and hunger contractions

Hunger contractions are produced as a result of *strong vagal stimulation to the stomach*. This occurs as follows : After several hours of fasting, hypoglycemia tends to occur and this activates the feeding centre in the hypothalamus which, in turn, stimulates the vagus nucleus in the medulla oblongata (refer to metabolism).

Hunger contractions are only associated with the sensation of hunger (hence the name), *but they are not its cause*. Hunger is felt as a result of *stimulation of the feeding and other higher centres*. Thus, *bilateral vagotomy only abolishes hunger contractions but not the hunger sensation*.

Factors that control (affect) gastric emptying

(1) **Type of food** : Carbohydrates leave the stomach in a few hours while proteins leave more slowly and fats are the slowest to be emptied.

(2) **Gastric factors** :

(a) *Degree of gastric distention* : Within limits, the greater the volume of the gastric content, the more rapid will be the rate of its emptying. Distention of the stomach initiates both *vago-vagal and local enteric reflexes* that stimulate gastric peristalsis and accelerate gastric emptying.

(b) *Consistency of the gastric contents* : Fluids are evacuated more rapidly than solid foods (which must be first converted to fluid chyme).

(3) **Duodenal factors** :

(a) *Degree of duodenal distention* : Excessive duodenal distention delays gastric emptying through the enterogastric reflex (page 20).

(b) *Type of food in the duodenum* : Presence of excess fat in the duodenum delays gastric emptying through stimulating release of the hormones that inhibit gastric motility (page 20). This effect is important since *fats are much slowly digested than most other kinds of food*.

(c) *Duodenal acidity* : Excessive duodenal acidity delays gastric emptying by both stimulating release of the gastric inhibitory hormones and initiating the enterogastric reflex (page 20).

(d) *Duodenal osmolality* : Hyperosmolality and hypoosmolality (to a lesser extent) stimulate certain *duodenal osmoreceptors* that lead to delayed gastric emptying mainly through initiating *the enterogastric reflex*. Such effect is important since it prevents rapid flow of non-isotonic fluids into the small intestine (which disturbs the electrolyte balance).

(4) **Other factors** :

(a) Stimulation of *pain receptors* (somatic or visceral) results in reflex inhibition of the gastric motility (thus delaying its emptying).

(b) *Emotional states* : Excitement, anxiety and anger accelerate gastric emptying while fear and depression slow it.

(c) *Chemical factors* : Gastric emptying is accelerated by cholinergic drugs, alcohol, bicarbonate and coffee while it is delayed by adrenergic drugs, atropine and excessive smoking.

Effects of gastrectomy (= removal of the stomach)

(1) *Loss of the storage function of the stomach* (so gastrectomized patients have to eat frequent small meals).

(2) *Pernicious anaemia* (due to absence of the intrinsic factor). The patients are also liable to develop *iron deficiency anaemia and weak bones due to absence of HCl* (page 25).

(3) *Normal digestion* (but with rather some difficulty since food reaches the duodenum in a solid form).

(4) *The dumping syndrome* : This is a distressing syndrome that sometimes occurs *after meals* and is characterized by (a) Abdominal discomfort due to sudden stretching of the duodenum (b) Hyperglycemia due to rapid absorption of glucose, followed about 2 hours later by hypoglycemia due to sudden increase in insulin secretion (c) Weakness, dizziness and sweating, partly due to hypoglycemia and partly due to hypovolemia and hypotension (which occur due to withdrawal of extra-cellular fluid into the gut by effect of the hypertonic substances in food).

VOMITING

This is reflex expulsion of the gastric contents outwards through the mouth and it often starts with the sensation of *nausea*.

MECHANISM OF VOMITING

The act of vomiting is controlled by a *vomiting centre* located in the medulla oblongata. Excitation of this centre leads to the following effects that result in vomiting (through discharging impulses in the 5th, 7th, 9th, 10th and 12th cranial nerves and the spinal nerves that supply the diaphragm and abdominal muscles) :

(1) *Forced inspiration* (which moves the diaphragm downwards)
 (2) *Closure of the glottis and elevation of the soft palate* to prevent the vomitus to enter the trachea and nasal cavities (as occurs in deglutition).

(3) *The body of the stomach and cardiac sphincter relax* while the pyloric antrum contracts at the incisura angularis (figure 18).

(4) *The abdominal wall muscles contract*. This together with the downward movement of the diaphragm markedly increase the intraabdominal pressure.

(5) The raised intra-abdominal pressure *squeezes the relaxed stomach* leading to ejection of its contents into the esophagus then outwards.

****** Nausea is usually associated with pallor, excessive salivation and sweating and *antiperistalsis may occur in the small intestine* (which drives its contents into the stomach).

CAUSES OF VOMITING

There are 2 main causes of vomiting :

(A) **Reflex vomiting** : This may occur as a result of either :

(1) **Conditioned reflexes** (= *psychic vomiting*) e.g. certain scenes or nauseating smells may induce vomiting.

(2) **Unconditioned reflexes** : A wide variety of conditions initiate signals that are discharged via afferent nerves to the medulla oblongata where they stimulate the vomiting centre, resulting in vomiting e.g. :

(a) Gastric irritation, peritonitis and intestinal obstruction (by impulses discharged in afferent sympathetic and parasympathetic nerve fibres).

(b) Irritation of the posterior part of tongue and oropharynx.

(c) Myocardial infarction.

(d) Motion sickness (by impulses from the semicircular canals).

(B) **Central vomiting** : Certain nervous diseases (e.g. meningitis, migraine and increased intracranial tension) and drugs (eg. apomorphine and digitalis) induce vomiting by exciting the vomiting centre. These drugs are called *emetic drugs* and they do not stimulate the vomiting centre directly. They first stimulate a nearby area in the medulla called the *chemoreceptor trigger zone (CTZ)* which, in turn, stimulates the vomiting centre. Stimulation of the semicircular canals induces vomiting also by stimulating the CTZ. Stimulation of this zone is also the cause of vomiting in *pregnancy, uremia and diabetic ketoacidosis*.

FUNCTION OF VOMITING

In cases of irritation of the upper part of the GIT (which is the commonest cause of vomiting), vomiting provides *rest and helps to drive out the irritant*. However, in many conditions, vomiting performs *no function* e.g. in pregnancy, myocardial infarction and motion sickness.

Effects of excessive (or prolonged) vomiting

(1) Dehydration. (2) Loss of electrolytes (specially Na^+ and K^+).

(3) Alkalosis, due to loss of H^+ (HCl).

Treatment of vomiting

(1) Treatment of the cause. (2) Vomiting can be stopped by certain drugs that inhibit the vomiting centre (= *anti-emetic drugs*) e.g. chlorpromazine.

(3) The effects of vomiting can be corrected by supplying fluids, electrolytes (specially K^+) and acidifying salts (to prevent alkalosis).

EXAMINATION OF THE STOMACH

Examination of the stomach can be achieved by (1) **Gastroscopy** which is greatly helpful in diagnosis of gastric diseases (2) **X- ray after taking a barium meal (barium sulphate solution)**.

Studying gastric functions by tests like the fractional test meal, the insulin test and the histamine test is no longer used now.

CHAPTER 4

THE PANCREAS

The pancreas is a gland that contains 2 parts : *an endocrine part and an exocrine part*. The endocrine part consists of the *islets of Langerhans* which secrete the hormones *insulin and glucagon*. On the other hand, the exocrine part consists of a *compound acinar gland that secretes the pancreatic juice* (which is collected by a system of ducts). The small ducts (or ductules) drain into a main large duct which *joins the common bile duct* forming the *ampulla of Vater* (or ampulla of the bile duct). This *opens into the duodenum* (figure 19), and its opening is controlled by the *sphincter of Oddi*. The pancreas receives parasympathetic (vagal) nerve fibres and sympathetic nerve fibres from the greater splanchnic nerves.

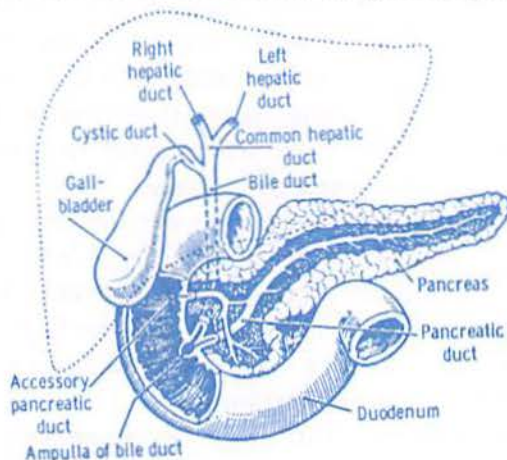


Figure 19 : The pancreas and biliary system.

THE PANCREATIC JUICE

This juice is the *most important digestive juice* and its daily volume is about *1500 ml*. It is *alkaline* (having a pH about 8) because of its high HCO_3^- content (see below), and is formed of 2 parts :

(1) **An aqueous part :** This is a watery juice rich in HCO_3^- that is secreted by the ductule cells. It also contains other anions (Cl^- , SO_4^{2-} and HPO_4^{3-}) and many cations (Na^+ , K^+ , Ca^{2+} and Mg^{2+}). Its HCO_3^- content (together with those in the intestinal juice and bile) neutralize HCl that is delivered from the stomach. This is important because (a) It produces a neutral (or slightly alkaline) pH in the intestine, which is optimum for activity of the pancreatic and intestinal enzymes (b) It protects the delicate duodenal mucosa from the harmful effects of HCl.

(2) **An enzymatic part :** This is a viscid juice secreted by the pancreatic acini, and is rich in digestive enzymes (see below)

Mechanism of HCO_3^- secretion

This occurs as follows : In the ductule cells, CO_2 combines with H_2O by activity of the *carbonic anhydrase enzyme* forming H_2CO_3 , which dissociates into H^+ and HCO_3^- . H^+ is transported into the blood in exchange for Na^+ , which is actively secreted into the lumens of the ductules together with HCO_3^- (forming NaHCO_3).

THE PANCREATIC ENZYMES

(1) Proteolytic (= protein-splitting) enzymes

These are normally secreted as *inactive proenzymes* and they become activated only in the small intestine. They include the following :

(a) **Trypsinogen** : This is activated to trypsin in the small intestine by an enzyme secreted by the duodenal mucosa called *enterokinase* (or *enteropeptidase*). Trypsin is an *endopeptidase*, and it also activates other enzymes (see below) as well as trypsinogen itself (*autoactivation*) .

(b) **Chymotrypsinogens** : These are *activated by trypsin* into chymotrypsins, which are also *endopeptidase enzymes*.

(c) **Proelastase** : This is *activated by trypsin* into elastase, which is also an *endopeptidase enzyme* that acts mainly on elastin.

(d) **Procarboxypeptidases** : These are *activated by trypsin* into carboxypeptidases, which are *exopeptidase enzymes* that act at the ends of the polypeptide molecules leading to release of amino acids.

(2) Lipolytic (= lipid-splitting) enzymes

(a) **Pancreatic lipase** : This is an *active enzyme* that hydrolyzes triglycerides into monoglycerides and fatty acids. Its action is facilitated in the presence of bile salts (which also help fat emulsification). However, the enzyme cannot penetrate the fat droplets which are covered by emulsifying agents. The pancreas also secretes a protein (enzyme) called *precolipase that is activated by trypsin into colipase* which displaces these emulsifying agents (thus allowing for the lipase action).

(b) **Phospholipase A₂** : This is *activated by trypsin* into phospholipase A₂ which acts on phospholipids resulting in formation of fatty acids and lysophospholipids (e.g. it changes lecithin into lysolecithin).

(c) **Cholesteryl ester hydrolase** : This hydrolyzes cholesteryl esters in the intestinal lumen leading to liberation of free cholesterol.

(3) Pancreatic alpha-amylase

This is an *active enzyme* that splits starch into maltose, maltotriose and alpha limit dextrins. It completes the action of salivary amylase (ptyalin) but it is *more potent* and it acts on both *cooked and uncooked starch*.

(4) Pancreatic nucleases

These include *ribonuclease and deoxyribonuclease enzymes*, which act on RNA and DNA, leading to formation of *nucleotides*.

****** All pancreatic proteolytic enzymes are secreted in an inactive form to protect the pancreas against *autodigestion*, and they become activated only in the small intestine under the effect of trypsin. Normally, some trypsinogen is activated to trypsin in the pancreas, but this is rapidly blocked by a *trypsin inhibitor* that is also secreted by the pancreas.

****** Obstruction of the main pancreatic duct may result in *acute pancreatitis* (severe inflammation of the pancreas). In this condition, the level of activated trypsin inside the pancreas may increase to a level high enough to activate other proteolytic enzymes, and all these enzymes attack the pancreatic tissue leading to its autodigestion. This is often accompanied by hemorrhage and severe pain (which may precipitate a fatal shock).

CONTROL OF SECRETION OF THE PANCREATIC JUICE

(A) NERVOUS CONTROL

The nervous control pancreatic secretion is primarily produced by the *parasympathetic (vagal) nerve supply* [*sympathetic stimulation decreases the pancreatic secretion by acting on alpha-adrenergic receptors*].

Vagal impulses mainly stimulate the acinar cells producing a secretion *rich in digestive enzymes and poor in fluid*. On taking a meal, the pancreatic secretion is initially stimulated under influence of vagal stimulation, and this occurs in 2 phases :

(1) **Cephalic phase** : This accompanies the cephalic phase of gastric secretion and, similarly, is the result of both *conditioned and unconditioned reflexes* (page 18).

(2) **Gastric phase** : This accompanies the gastric phase of gastric secretion, and is the result of both the *vagovagal reflex* that is initiated from the stomach (page 19) as well as the released *gastrin hormone* (which weakly stimulates pancreatic secretion).

(B) HORMONAL CONTROL

2 gastrointestinal hormones control secretion of the pancreatic juice :

(1) **Secretin** : This hormone is secreted by the duodenal mucosa *in response to the acid chyme* delivered from the stomach. It *stimulates secretion of the aqueous part* of the pancreatic juice from the ductule cells (which is rich in water, HCO_3^- and other electrolytes). Such secretion is essential for *neutralization of the acid chyme* in the duodenum.

(2) **Cholecystokinin-pancreozymin (CCK)** : This hormone is secreted by the duodenal mucosa *in response to the digestive products of proteins and fats*. It *stimulates secretion of the enzymatic part* of the pancreatic juice from the acinar cells (*similar to vagal stimulation*).

****** Kinins (which are potent V.D. polypeptides) are liberated during pancreatic activity, and they may be responsible for the increased blood flow that accompanies pancreatic secretion.

Effects of extirpation (= damage) of the pancreas

- (1) **Diabetes mellitus** due to lack of insulin (refer to endocrine glands).
- (2) **Digestive and nutritional disturbances** : The various food constituents are not properly digested leading to deficient absorption and loss of considerable amounts of the ingested protein and fat in the feces. Fat loss causes *steatorrhea* (= *fatty diarrhea*) in which the feces becomes bulky, pale, loose and greasy, and the result is marked *undernutrition*.

Effects of loss of the pancreatic juice

This often occurs *secondary to severe diarrhea*, and it leads to :

- (1) Marked digestive and nutritional disturbances (see above)
- (2) Dehydration due to the large volume of the juice
- (3) Acidosis due to loss of NaHCO_3 .

Examination of the pancreas

Examination of the pancreas can be achieved by :

- (1) **Ultrasonography** : This is specially helpful in detection of pancreatic masses.
- (2) **Stool analysis** : In cases of pancreatic insufficiency, the stool contains excessive amounts of undigested protein and fat (= *steatorrhea*) and becomes bulky, pale, loose and greasy.
- (3) **Estimation of the amylase and lipase blood levels** : These enzymes are *normally present in the blood but in very small amounts*. They are markedly increased in conditions of *pancreatic duct obstruction* and in cases of *acute pancreatitis* (page 33) particularly amylase.

Studying pancreatic functions by tests like the secretin test and analysis of the duodenal contents is no longer used now.

BILE AND GALLBLADDER

Functional anatomy of the biliary system

Bile is an important juice that is *secreted by the liver and stored in the gallbladder*. The liver cells secrete bile into fine biliary canaliculi which coalesce together forming *the right and left hepatic ducts* (one from each lobe of the liver). These join outside the liver forming the *common hepatic duct*, which unites with the *cystic duct of the gallbladder* forming the *common bile duct*. This joins the main pancreatic duct forming the *ampulla of Vater* which opens at the duodenal papilla, and its opening is controlled by the *sphincter of Oddi* (figure 20).

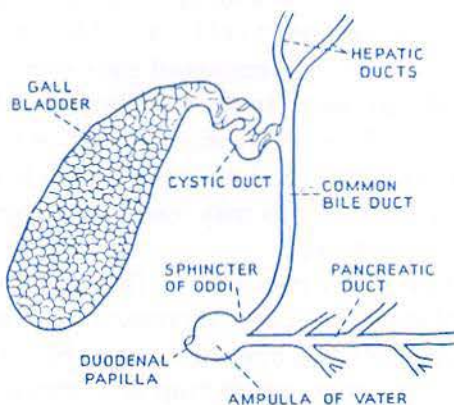


Figure 20 : Anatomy of the biliary system.

Composition of liver bile

The liver bile (obtained from the hepatic ducts) is a *golden-yellow alkaline fluid* (pH 7.8 - 8.6). Its volume is about **500 ml daily**. It is composed of water (97 %) containing both organic and inorganic constituents as well as the *alkaline phosphatase enzyme*. The organic constituents are chiefly *bile salts and bile pigments* together with small amounts of *cholesterol, fatty acids, lecithin and fat*. The main cations are Na^+ , K^+ and Ca^{2+} , while the main anions are Cl^- and HCO_3^- .

The bile salts and bile pigments as well as most cations are *actively transported across the membranes of the bile canaliculi*. On the other hand, HCO_3^- is primarily secreted by the *biliary duct cells*, and it shares in neutralization of the gastric HCl in the duodenum. The main stimulus for biliary HCO_3^- secretion is the *secretin hormone*.

FUNCTIONS OF THE GALLBLADDER

(1) **Storage of bile** : Between meals the sphincter of Oddi is tonically contracted, so bile flows retrograde upwards through the cystic duct to be stored in the gallbladder.

(2) **Concentration of bile** : The capacity of the gallbladder is only 20-60 ml, and to accommodate the large volume of bile flowing from the liver, bile concentration takes place in the gallbladder. Its mucosa actively reabsorbs Na^+ and this is followed by passive reabsorption of water and HCO_3^- as well as the other electrolytes (except Ca^{2+}). Accordingly, the concentration of bile salts in the gallbladder bile increases 5-10 times more than that in the liver bile, and its water content becomes only 89 % (in contrast to 97 % in the liver bile).

(3) **Acidification of bile** : This occurs as a result of HCO_3^- reabsorption during bile concentration (see above). It decreases the pH of the gallbladder bile to 7 - 7.4 (in contrast to pH 7.8 - 8.6 of the liver bile) which prevents Ca^{2+} precipitation and formation of gallstones.

(4) **Decreasing the pressure in the bile ducts** : This occurs because the gallbladder accommodates a considerable part of the liver bile that is secreted between meals (when the sphincter of Oddi is closed). Excessive rise of pressure in the biliary ducts may lead to stoppage of bile secretion and impairment of liver functions.

(5) **Secretion of mucus (white bile)** : This is secreted by the mucous glands in the gallbladder mucosa. It protects the gallbladder mucosa against the highly concentrated bile salts, gives bile a semifluid consistency and, in the small intestine, it acts both as a lubricant and as a buffer.

(6) **Evacuation** : The gallbladder has to evacuate its contents into the duodenum in addition to its functions. Such function is achieved by contraction of its wall and relaxation of the sphincter of Oddi (see below).

FACTORS THAT AFFECT BILE FLOW

(1) **Hepatic blood flow** : Bile secretion and flow is directly proportional to the hepatic blood flow rate.

(2) **Vagal stimulation** : This increases bile flow through liberating acetylcholine which (a) Produces V.D. and increases the hepatic blood flow (b) Shares in gallbladder emptying (see below).

(3) **Bile salts** : On reaching the intestine, 90-95 % of the bile salts are actively reabsorbed at the terminal ileum into the portal vein, which carries them back to the liver (= *enterohepatic circulation of bile salts*). The bile salts stimulate formation of more bile by the liver and are rapidly resecreted leading to increased flow of bile (= *a choleric effect*).

(4) **Hormones** : The hormone *secretin* stimulates secretion of HCO_3^- and water by the biliary duct cells, leading to increased flow of bile (= *a hydrocholeric effect*).

(5) **Gallbladder emptying (evacuation)** : This markedly increases bile flow, and it is controlled by nervous and hormonal mechanisms (see next).

Control of gallbladder emptying (evacuation)

(1) **Nervous control** : Stimulation of the *vagus nerve* causes contraction of the gallbladder wall, thus sharing in its evacuation and increasing bile flow into the duodenum (also due to increasing bile secretion by producing V.D. in the liver). Vagal stimulation normally occurs on taking a meal through both *conditioned and unconditioned reflexes* during the cephalic phase of gastric secretion.

(2) **Hormonal control** : The hormone *CCK* causes strong contraction of the gallbladder wall leading to evacuation of its contents into the duodenum. It is released by the duodenal mucosa in response to the digestive products of foods, specially the fatty foods (so after a fatty meal, the gallbladder empties completely in about 1 hour).

CHOLERETICS AND CHOLAGOGUES

These are substances that *increase bile flow into the duodenum*.

Choleretics

These are substances that increase bile flow through *increasing its formation by the liver*. The physiologic (natural) choleretics include (a) The *bile salts* (the most potent) (b) The *secretin hormone* which is hydrocholeretic (see above). Certain drugs also act as choleretics e.g. the V.D. drugs which increase the hepatic blood flow.

Cholagogues

These are substances that cause *contraction of the gallbladder wall* leading to its evacuation and increased flow of bile. *Magnesium sulphate* acts as a cholagogue but the physiologic (= natural) cholagogue is the *hormone CCK*. These substances also relax the sphincter of Oddi.

Examination of the gallbladder

This can be achieved by the following methods :

- 1- *Ultrasonography* . 2- *Tomography (CT)* .
- 3- *Nuclear cholescintigraphy* (gallbladder visualization by isotopes).
- 4- *Cholecystography* (gallbladder visualization by x-ray). The subject is given an i.v. dose of a *radio opaque dye* (usually an iodine-containing dye) which will be excreted by the liver in bile then it becomes concentrated in the gallbladder, so it will be clearly seen in x-ray (figure 21 left). Its rate of emptying can be investigated by giving the subject a fatty meal then taking *successive x-rays*. Normally, the size of the gall-bladder decreases to less than 1/3 of its original size within 30 minutes (figure 21 right).

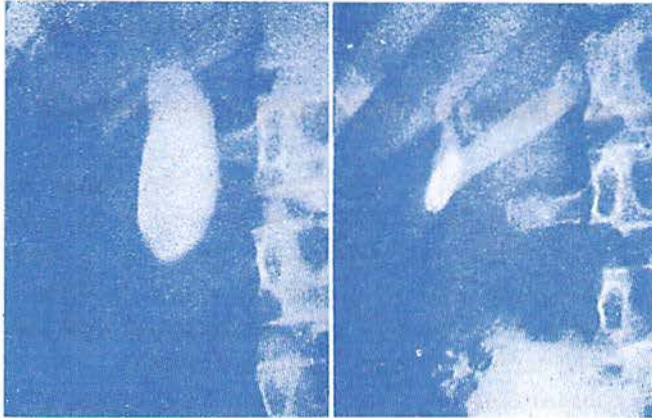


Figure 21 : Normal x-rays of the gallbladder before a fatty meal (left) and half an hour after it (right).

FUNCTIONS OF BILE

In addition to the functions of the *bile salts* (see below), bile performs the following functions :

- (1) Its HCO_3^- content shares in *neutralization of HCl* in the duodenum (with the pancreatic and intestinal juices).
- (2) Its mucin content (white bile) acts both as a *lubricant*, and as a *buffer* in the small intestine.
- (3) It is an *excretory route* for (a) Bile pigments (which have no functions) (b) Certain heavy metals, toxins and bacteria (c) The alkaline phosphatase enzyme (d) Cholesterol and lecithin.

THE BILE SALTS

Chemical nature and formation

Several bile acids are synthesized in the liver from cholesterol, mostly cholic acid. This acid is conjugated to glycine and taurine, forming glycocholic and taurocholic acids. Bile salts are the *Na and K salts of these acids* (i.e. Na and K glycocholate and taurocholate).

Enterohepatic circulation of bile salts

About 90- 95 % of the bile salts are actively reabsorbed at the *terminal ileum*. These are returned to the liver where they are re-secreted, while the remaining 5-10 % enter the colon and are mostly excreted in the stool.

The total amount of bile salts in the body is about 3.5 gm. These salts recycle via the enterohepatic circulation 6-8 times daily and the amount lost daily (0.2-0.4 gm) is replaced by new synthesis in the liver. If the enterohepatic circulation is interrupted, most bile salts are lost in the stool, and the liver in this case cannot compensate for the loss, and signs of bile salt deficiency will ultimately appear (see below).

Functions of bile salts

- (1) They help **fat (lipid) digestion** by the following ways :
 - a- They reduce the surface tension of fats, leading to **fat emulsification** (= detergent function of bile salts) which exposes larger areas of fats for the action of the lipase enzymes.
 - b- They **activate the lipase enzymes** in the small intestine.
- (2) They are essential for **fat absorption by their hydrotropic effect**. They combine with lipids to form water-soluble complexes called **micelles** from which fats are more easily absorbed (refer to chapter 10).
- (3) They are essential for **absorption of the fat-soluble vitamins** (= **vitamins A, D, E and K**) which are absorbed along with fats.
- (4) They are the **most potent choleretic substances** (page 38).
- (5) They exert **a laxative action** by stimulating intestinal peristalsis.
- (6) They are essential for **keeping cholesterol dissolved in bile**, thus preventing its precipitation and formation of cholesterol stones.
- (7) They **indirectly prevent protein putrefaction** by the intestinal bacteria (the enhanced fat digestion and absorption allows better protein digestion, so negligible amounts of undigested proteins reach the colon and no putrefaction occurs).

THE BILE PIGMENTS

These are the **end-products of hemoglobin (Hb) metabolism**. The old R.B.C.s are taken up by the cells of reticuloendothelial system in which Hb is split into heme and globin. The iron in heme is separated and stored in the liver and bone marrow while the remaining part is converted to a green pigment called **biliverdin**. This is reduced into a yellow pigment called **bilirubin**, which enters the bloodstream and becomes bound to albumin forming a compound called **hemobilirubin** (= **unconjugated, indirect or free bilirubin**). This is the chief form of bilirubin in the blood, and it is extracted actively by the liver cells, in which albumin is detached while bilirubin is conjugated mainly with glucuronic acid forming a compound called **cholebilirubin** (= **conjugated bilirubin or direct bilirubin**). This is actively transported into the bile canaliculi which transport them to the small intestine. However, *a small amount of cholebilirubin escapes into the bloodstream and is then excreted in the urine* (figure 22).

In the large intestine, a considerable amount of the conjugated bilirubin is changed by bacterial action into a colourless substance called **urobilinogen** most of which is excreted in the stool as **stercobilinogen** and this is oxidized to a brown substance called **stercobilin** when exposed to air (giving the stool its normal colour). The remaining part is reabsorbed in the portal vein to the liver where it is mostly re-excreted in bile again (= **entotohepatic circulation of bile pigments**). However, a small amount (about 5 %) enters the general circulation and is excreted in the urine, in which it is oxidized to **urobilin** on exposure to air (figure 22).

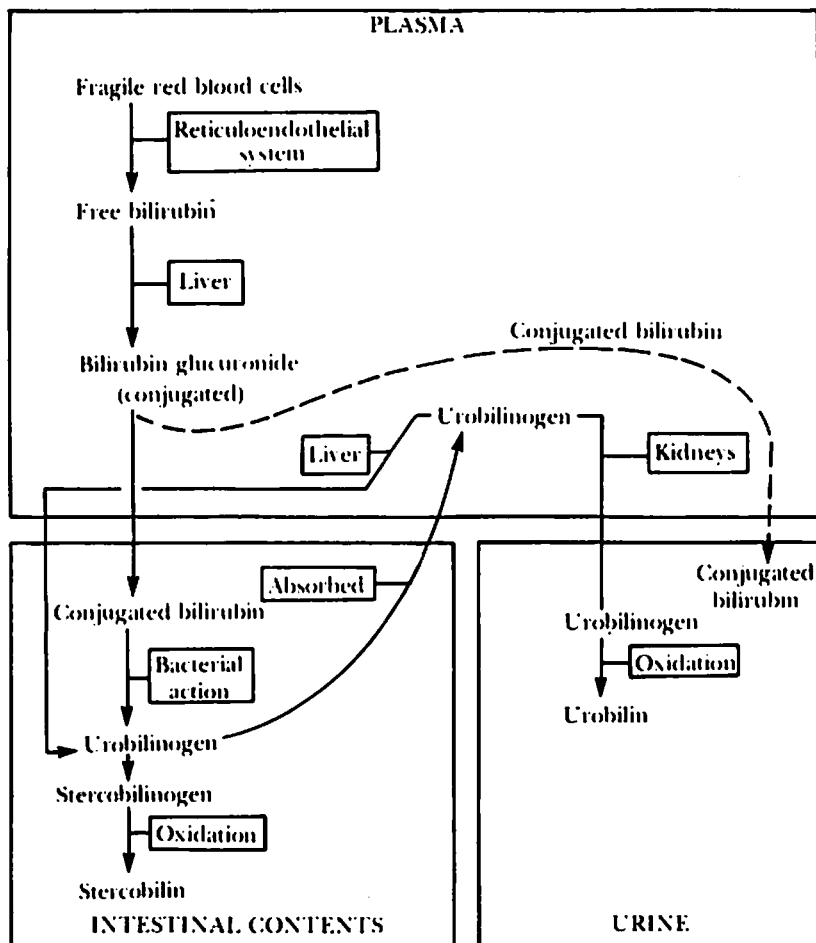


Figure 22 : Bilirubin formation and excretion.

****** There is an enterohepatic circulation for both bile salts (page 38) and bile pigments (mostly urobilinogen), and normally urine contains traces of both urobilinogen and conjugated bilirubin, while the stool contain a large amount of stercobilinogen and some conjugated bilirubin.

JAUNDICE (ICTERUS)

This is a disease characterized by a *yellowish colouration* of the skin, mucous membranes and sclera of the eye due to presence of excessive amounts of bilirubin in the blood.

Normally, the chief bile pigment in the serum is hemobilirubin together with trace amounts of cholebilirubin and urobilinogen (see above) and the total bilirubin serum level is normally 0.5 (up to 1) mg %. *Jaundice appears when this concentration rises to 1.5 - 2 mg %*. Depending on the cause, jaundice can be classified into 3 types :

(A) Hemolytic (prehepatic) jaundice

This occurs as a result of *excessive hemolysis* (= breakdown of the R.B.C.s). This may occur physiologically during the first week in newly born infants or in certain diseases e.g. hereditary spherocytosis, sickle cell anemia and erythroblastosis fetalis. The rate of synthesis of hemobilirubin is increased, so it accumulates in the blood. This type is characterized by :

- (1) Increased amount of hemobilirubin in the blood (cause of jaundice).
- (2) Increased formation of cholebilirubin in the liver. This leads to increased formation of urobilinogen and accordingly, excess urobilinogen is excreted in the urine and excess stercobilinogen is excreted in the stool (so the *stool colour becomes very dark brown*).

- (3) The urinary content of bilirubin is not significantly increased because hemobilirubin is cannot filtered through the renal glomeruli (= *acholuric jaundice*) and a *whitish foam* is produced on shaking the urine,.

- (4) *Normal fat digestion and absorption as well as liver functions.*

- (5) *Blood changes* : There are (a) *Anemia* (due to the excessive hemolysis) (b) Increased number of *reticulocytes* due to the increased activity of the bone marrow (c) the *abnormality that caused excessive hemolysis* (e.g. spherocytes or sickle cells).

(B) Hepatocellular (hepatic) jaundice

This occurs as a result of damage of the liver cells commonly due to either infection (hepatitis) or certain toxic drugs. It is characterized by :

- (1) *Impaired liver functions*, which leads to (a) Decreased extraction of hemobilirubin from the blood (so its plasma level increases) and decreased formation of cholebilirubin, so the formation of urobilinogen in the intestine is also decreased leading to decreased excretion of stercobilinogen in the stool (so the *stool colour becomes pale*). (b) Decreased secretion of the bile salts, which leads to disturbances in fat digestion and absorption.

- (2) *Mild biliary obstruction* due to swelling of the liver cells, which leads to *regurgitation of some cholebilirubin into the bloodstream* (thus, *the plasma levels of both hemobilirubin and cholebilirubin are increased*).

- (3) The *urine colour becomes darker than normal* due to presence of excess cholebilirubin in the blood (which can be filtered through the renal glomeruli), so a *yellowish foam* is produced on shaking the urine.

(C) Obstructive (posthepatic) jaundice

This occurs as a result of *obstruction of the common bile duct* (commonly due to *gallstones or cancer head of the pancreas*), which leads to decreased flow of bile into the intestine and its stagnation in the biliary passages (= *cholestasis*) followed by regurgitation into the bloodstream. This type is characterized by :

- (1) Severe jaundice due to increased plasma level of *cholebilirubin* as a result of its regurgitation into the bloodstream.
- (2) *Impaired liver functions* as a result of pressure on the liver cells by the stagnated bile.
- (3) *The stool colour is very pale* due to deficient formation of urobilinogen in the intestine.
- (4) *The urine colour is very dark* because it contains excess cholebilirubin which is filtered through the renal glomeruli (but its urobilinogen content is low) so *an intense yellow foam* is produced on shaking the urine.
- (5) *Marked disturbances in fat digestion and absorption* due to decreased flow of bile salts into the intestine, as well as *pruritis* (= *itching*) and *bradycardia* due to rise of the bile salts plasma level as a result of their regurgitation into the bloodstream (see below).
- (6) Marked rise of the plasma levels of both *cholesterol and the alkaline phosphatase enzyme* as a result of their regurgitation into the bloodstream.

Effects of obstruction of the common bile duct

- (1) *Obstructive jaundice* (see above).
- (2) *Impaired liver functions* (due to back pressure on the liver cells).
- (3) *Decreased flow of bile salts into the intestine*, which causes :
 - (a) Deficient fat digestion and absorption: As much as 50 % of the ingested fat is lost in feces leading to *steatorrhea* (= *fatty diarrhea*).
 - (b) Deficient absorption of fat-soluble vitamins (vitamins A, D, E, K) leading to signs of their deficiency.
 - (c) Protein putrefaction (page 39).
 - (d) Constipation (due to absence of the laxative effect of bile salts).
- (4) *Pruritis* (= *itching*) and *bradycardia* : These are produced by the excessive amounts of *bile salts* in the bloodstream (as a result of their regurgitation from the bile canaliculi). Bradycardia is due to inhibition of the S.A. node of the heart and probably also stimulation of the cardio-inhibitory centre in the medulla oblongata.

VAN DEN BERG TEST

This is a test that *differentiates the 3 types of jaundice*. A reagent called *Erlich 's (or diazo) reagent* is added to the patient's serum followed by addition of *alcohol*, and the result is interpreted as follows :

- (1) If a *direct reaction* is obtained (indicated by rapid appearance of a *pink colour that is not deepened by alcohol*), the condition is *obstructive jaundice*. The direct reaction occurs because the serum in this case

contains **excess cholebilirubin** which reacts directly with the reagent.

(2) If an **indirect reaction** is obtained (i.e. appearance of the pink colour **only after addition of alcohol**), the condition is **hemolytic jaundice**. This is because the **excessive serum hemobilirubin** in this case is bound to albumin, and the latter prevents its direct reaction with the reagent (but after addition of alcohol, bilirubin is released from albumin and the reaction takes place).

(3) In case of **hepatic jaundice**, a **biphasic reaction is obtained** i.e. a faint pink colour appears on addition of the reagent to the serum (due to presence of **cholebilirubin**) which is deepened on addition of alcohol (due to presence of **hemobilirubin** as well).

**** With normal serum, the test is negative** (i.e. no colour appears after addition of either the reagent or alcohol).

The following table shows the differences between the 3 types of jaundice

	Hemolytic j.	Obstructive j.	Hepatic j.
Cause	Excessive R.B.C.s breakdown	Obstruction of the common bile duct	Liver disease
Cause of yellow colour	Increased serum hemobilirubin	Increased serum cholebilirubin	Increased serum cholebilirubin and hemobilirubin
Depth of colour	Mild	Severe	Moderate
Van Den Berg test	Indirect	Direct	Biphasic
Fat digestion	Normal	Markedly impaired	Moderately impaired
Liver functions	Normal	Moderately impaired	Markedly impaired
Urine colour	Normal (acholuric)	Dark brown	brownish
Urine foam	White	Intense yellow	Yellowish
Stool colour	Dark	Very pale	Pale
Blood	Anemia, reticulocytosis and may be the cause of hemolysis	Marked Increase in cholesterol, alkaline phosphatase and bile salts	Moderate increase in cholesterol, alkaline phosphatase and bile salts

CHAPTER 6

THE LIVER

The liver is the largest gland in the body (weighing about 1.5 kg) and is *essential to life*. Its functional unit is the **lobule** (of which there are 50000-100000 in the human liver). Each lobule consists of radiating columns of cells (= *hepatocytes*) around a central vein and these columns are separated by *blood sinusoids* (figure 23). The hepatic sinusoids are lined by flat endothelial cells and contain the large **Kupffer cells** (tissue macrophages or reticuloendothelial cells). The sinusoidal endothelium has *wide fenestrations* (pores), so it is extremely permeable.

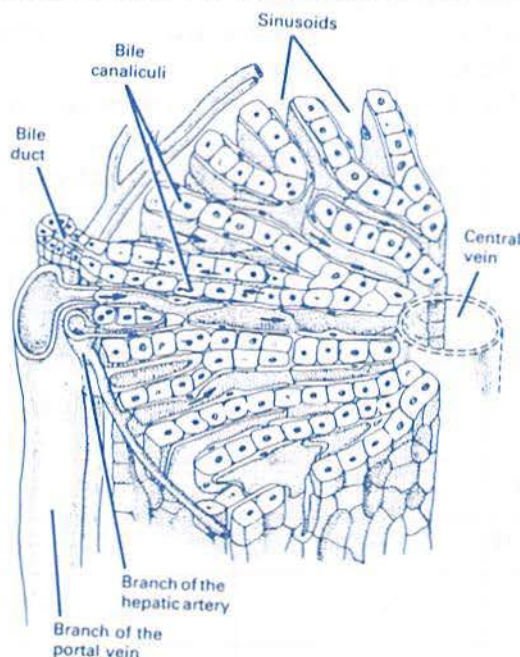


Figure 23 : Basic structure of a liver lobule.

THE HEPATIC VASCULAR SYSTEM

The liver receives about 1500 ml blood/minute (about 30% of the cardiac output) from 2 sources (a) *the portal vein* (1000-1100 ml) (b) *the hepatic artery* (350-500 ml). These pour blood into the sinusoids which drain into the *central veins*, and these coalesce forming *hepatic veins* which drain into the *inferior vena cava*. There is also a rich *lymph drainage* from the liver.

FUNCTIONS OF THE LIVER

The liver exerts many functions that can be classified as follows :

(1) Functions of the hepatic vascular system

(a) **Blood storage (reservoir function) :** The liver is an expandable organ that normally stores about 10 % of the total blood volume (450 ml) in the sinusoids and hepatic veins. When needed, this blood, can be added to the general circulation (e.g. in cases of severe hemorrhage).

(b) **Blood filtration :** The hepatic Kupffer cells engulf and digest 99 % of the bacteria that enter the portal blood from the intestine and also remove foreign and unrequired substances (e.g. the small blood clots).

(2) Bile formation

This includes synthesis and secretion of *bile salts*, and formation and excretion of *bile pigments*. The liver also performs other *synthetic and excretory functions* e.g. it synthesizes *25- hydroxycholecalciferol* as well as *most plasma proteins and clotting factors*, and excretes dyes such as bromsulphalein and tetraiodophenolphthalein.

(3) Metabolic functions

(A) Carbohydrate metabolism

(a) The liver converts galactose and fructose to glucose (which is the form that can be utilized by the tissue cells).

(b) The liver is essential for maintaining a normal blood glucose level (= *glucostasis*). If the blood glucose level increases, the excess is taken by the liver and is converted to glycogen (*glycogenesis*) and fat (*lipogenesis*), and if it decreases, it is added by the liver into the bloodstream (through the processes of *glycogenolysis and gluconeogenesis*).

(B) Protein metabolism

(a) *Deamination of amino acids*, and the resulting products are either oxidized (to supply energy) or converted into carbohydrates and fats.

(b) *Conversion of ammonia to urea* : Ammonia is formed in the gut by bacteria and its conversion to urea is *life-saving* because it produces toxic effects specially to the nervous system (= *hepatic encephalopathy*).

(c) *Formation of uric acid* (end-product of nucleoprotein metabolism).

(d) *Synthesis of non-essential amino acids* (through transamination).

(e) *Synthesis of the plasma proteins* (except gamma-globulins).

(C) Fat metabolism

(a) *Oxidation of fatty acids to supply energy*. Neutral fat is first split into glycerol and fatty acids (= *lipolysis*), then the latter are split by beta-oxidation into acetyl radicles which combine with coenzyme A (CoA) forming *acetyl-CoA*. Part of acetyl-CoA is oxidized in the *citric acid cycle* while the other part is converted by condensation of 2 molecules into *acetoacetic acid* which is delivered by the liver cells to the bloodstream and is oxidized at other tissues.

(b) **Synthesis of cholesterol, lipoproteins and phospholipids.** 80 % of cholesterol is converted into bile salts, while the remainder (together with phospholipids and lipoproteins) is transported to the tissues. In the tissues lipoproteins are split and fat is stored or oxidized while phospholipids and cholesterol form cell membranes and certain intracellular organelles.

(c) Fat synthesis from carbohydrates and proteins (= **lipogenesis**).

(4) Storage functions

Besides storing blood, glycogen and fat, the liver also stores :

(a) **Vitamins**, particularly vitamins A, D and B₁₂ [in sufficient amounts for about 10 months, 3-4 months and 12 months respectively].

(b) **Iron**, which is stored in the liver cells in the form of **ferritin** (refer to blood). When the blood iron level decreases the liver ferritin releases its iron content to the blood while if the blood iron level increases, it is taken by the liver where it is stored (= **blood iron buffer function**).

Accordingly, **the liver is essential for erythropoiesis** (since it supplies vitamin B₁₂ and iron in addition to the **globin** fraction of hemoglobin). The erythrocytes are also formed in the liver during fetal life (refer to blood).

(5) Detoxification and inactivation functions

(a) Many drugs are detoxified in the liver (or excreted in bile) e.g. sulfonamides, penicillin, ampicillin and erythromycin. Similarly, many toxins are detoxified (e.g. benzoic acid salts are detoxified by conjugation to glycine forming hippuric acid).

(b) Several hormones are inactivated in the liver e.g. thyroxine, some polypeptide hormones & the steroid hormones (by reduction and conjugation). Accordingly, liver damage may lead to accumulation of these substances (drugs, toxins or hormones) in the body to high dangerous levels.

THE LIVER FUNCTION TESTS

(1) Tests depending on estimation of enzymes

The serum levels of the following enzymes increase in liver disease :

(1) **The transaminases** : These include 2 enzymes :

a- **Alanine aminotransferase (ALT)** : This is also called **GPT** (*glutamic pyruvic transaminase*) and its normal serum level is 3 - 48 units / litre.

b- **Aspartate aminotransferase (AST)** : This is also called **GOT** (*glutamic oxalacetic transaminase*) and its normal serum level is 0 - 55 units / litre.

(2) **The alkaline phosphatase** (normal level 13 - 39 units / litre).

(2) Tests depending on determination of the plasma proteins

(a) Determination of *serum albumin level* : This is decreased in liver disease (normal amount 3.1 - 4.3 gm %).

(b) Determination of *albumin/globulin (A/G) ratio* : This ratio (which is normally 1:2-1.6) is lowered in liver disease because albumin synthesis is decreased (refer to blood).

(c) Determination of *prothrombin level and prothrombin time* : In liver disease, the plasma prothrombin level (which is normally 10-15.mg %) is lowered and the prothrombin time (which is normally 12 seconds) is prolonged (see in blood) and such disorders are not corrected by vitamin K.

(3) Tests depending on metabolic functions

The galactose tolerance test :

The fasting subject ingests 40 gm galactose in 400 ml water and its blood level is determined every 1/2 hour for 2 hours. Normally, it rises slightly within one hour then falls within 2 hours, and the sum of the 4 values (= *-galactose index*) should not exceed 160 mg %. *Such index rises in cases of liver disease* due to inability of the liver to convert galactose to glucose.

(4) Tests depending on detoxification functions

The hippuric acid excretion test :

A test dose of Na benzoate is given to the subject (orally or i.v.) and the hippuric acid is estimated in the urine after one hour. Normally, its excretion should markedly increase, but in liver disease no or insignificant increase occurs because of inability of the liver to conjugate benzoate to glycine.

(5) Tests depending on hepatic excretory functions

(a) Determination of the *serum bilirubin level* : The total serum bilirubin level (conjugated and unconjugated) is normally up to 1 mg % while the level of conjugated bilirubin only is up to 0.4 mg %. Total bilirubin increases in liver disease mainly due to increased amount of the unconjugated part (*hemobilirubin*) as a result of failure of the liver cells to extract it from the blood. The conjugated part (*cholebilirubin*) level specially increases if there is intrahepatic biliary obstruction .

(b) *Bromsulphalein retention test* : Bromsulphalein is a dye that is excreted by the liver in bile. A test dose of this dye is i.v. injected and its concentration in the blood is estimated after one hour. Normally, only 0 - 3 % of the injected dose is retained in the blood, but in liver disease a greater amount is retained.

CHAPTER 7

THE SMALL INTESTINE

In the small intestine, complete food digestion occurs by the *intestinal and pancreatic juices as well as by bile, and the products of digestion are then absorbed together with most vitamins, minerals and fluids.*

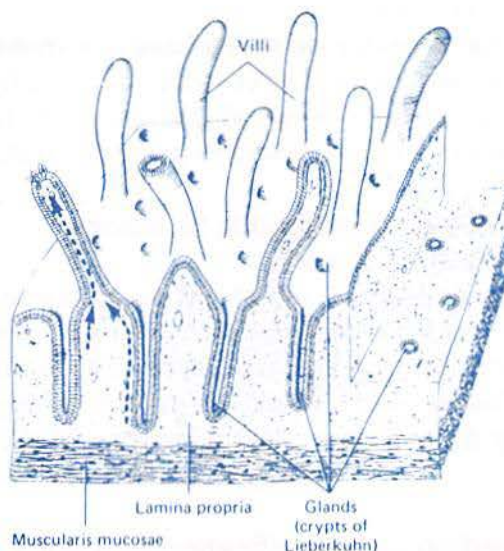


Figure 24 : Structure of the small intestinal mucosa.

THE INTESTINAL MUCOSA

The intestinal mucosa is formed of a single layer of columnar epithelial cells (= *enterocytes*), a connective tissue layer (= *lamina propria*) and *muscularis mucosae* (figure 24), and it has many valve-like folds called *valvulae conniventes* (figure 25). Its surface is characterized by finger-like projections called the *villi*, and it contains simple tubular glands called the *crypts of Lieberkuhn* (figure 24). The mucosa also contains solitary lymph nodules which become aggregated in the ileum forming *Peyer's patches*. In the duodenum, there are also small coiled glands called *Brunner's glands* which secrete thick alkaline mucus. In the crypts there are also *goblet cells* which secrete mucin and *paneth cells* which secrete **defensins** (naturally occurring peptide antibiotics).

There are 20-40 villi / mm² of the intestinal mucosa. Each villus is a finger-like projection (0.5-1 mm long) that contains a network of capillaries and a lymph vessel called the *central lacteal* (figure 26 left), as well as a fine extension of the muscularis mucosae. The free edges of the columnar cells that cover the villi contain microvilli (which form a *brush border*) and the cells are connected by *tight junctions* (figure 26 right).

The presence of the *valvulae conniventes*, villi and microvilli *increases*

the absorptive surface of the small intestine to about 200 m^2 (i.e. about 600 times the real surface area of the small intestine).

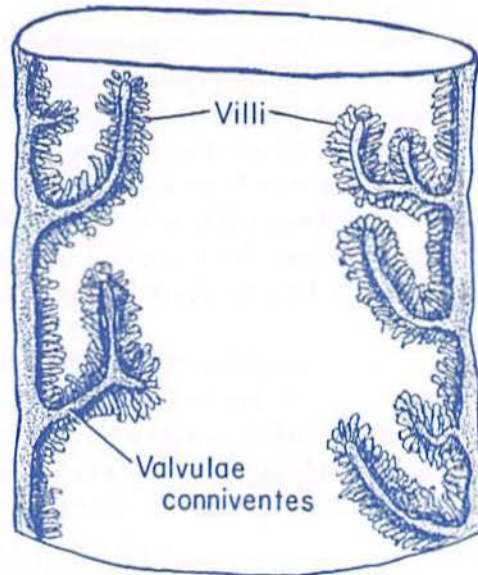


Figure 25 : Mucosal folds in the small intestine (= valvulae conniventes).

THE INTESTINAL JUICE (= SUCCUS ENTERICUS)

The normal volume of this juice is about *1 litre / day*, and it contains :

(1) *An alkaline fluid secreted by the crypts of Lieberkuhn* (pH 7.5). It is an *isotonic fluid* that contains mainly HCO_3^- but no digestive enzymes.

(2) *Mucus* : The mucus secreted by the surface epithelium and goblet cells covers, lubricates and protects the intestinal epithelium while that secreted by Brunner's glands (plus HCO_3^- secreted by the duodenal mucosa) also helps protection of the duodenal mucosa from the gastric HCl (specially at the first part known as the duodenal cap or bulb).

(3) *Mucosal cells* : Normally, large numbers of these cells are *sloughed* (=shed) daily into the intestinal lumen, then they are replaced by new cells formed from *mitotically-active undifferentiated cells located deep in the crypts* (which migrate up to the tips of the villi and live for 2-5 days then they are sloughed). As a result of such sloughing of the intestinal mucosal cells, about 30 gm of protein is "secreted" daily in the intestinal lumen.

The intestinal enzymes

These are *present in the membranes of the mucosal cells* (specially at their brush borders). Intestinal digestion occurs mainly at these brush borders where the enzymes catalyze food hydrolysis before absorption of the end products. The main intestinal enzymes include the following :

(1) **Enterokinase (enteropeptidase)** : This enzyme activates trypsinogen into trypsin. It is probably the *only enzyme present free in the succus entericus*, and its secretion is stimulated by CCK.

(2) **Peptidases (erepsin)** : These are *exopeptidase proteolytic enzymes* that act on polypeptides and small peptides releasing amino acids e.g. *dipeptidase and various aminopeptidases*.

(3) **Disaccharidases** : These act on disaccharides converting them into monosaccharides (the final step in carbohydrate digestion). They include :

(a) **Maltase**, which breaks down maltose and malto-triose into glucose.

(b) **Lactase**, which breaks down lactose into glucose and galactose.

(c) **Sucrase (= invertase)**, which breaks down sucrose into glucose and fructose.

(4) **Intestinal lipase** : This completes the action of the lingual, gastric and pancreatic lipases. However, *its presence is doubtful*.

(5) **Nucleases** : These include *nucleotidases* (which split nucleotides into nucleosides and phosphoric acid) and *nucleosidases* (which split nucleosides into their constituent sugars and purine and pyrimidine bases).

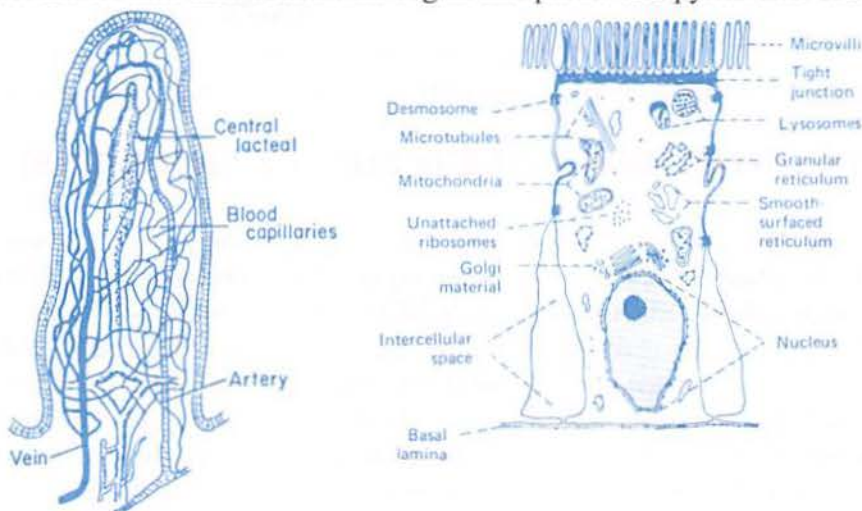


Figure 26 : Structure of an intestinal villus (left) and an enterocyte showing microvilli and tight junctions (right).

REGULATION OF INTESTINAL SECRETION

The intestinal secretion is regulated by the following :

(1) **Local stimuli** : Intestinal secretion occurs mainly in response to physical irritation (distention) and chemical irritation (by digestive products and acid chyme) both directly and through local enteric reflexes.

(2) **Nervous regulation** : Vagal stimulation increases mucus secretion specially from the Brunner's glands.

(3) **Hormonal regulation** : Secretin, VIP and CCK stimulate secretion from the crypts of Lieberkuhn. Secretin also stimulates secretion from the Brunner's glands.

INTESTINAL MOVEMENTS (MOTILITY)

Electric activity of the intestinal muscle

The intestinal muscle show rhythmic fluctuations in the membrane potential called the *basal electric rhythm (BER)* like that occurring in the stomach (page 27). This BER is initiated by certain pacemaker cells in the circular muscle layer called the *interstitial cells of Cajal*, and its rate is about 12 / minute in the duodenum and falls to about 8 / minute in the distal ileum. Spike potentials superimpose on the depolarizing portions of the BER. The depolarizing portions of these spikes are due to Ca^{2+} influx while their repolarizing portions are due to K^{+} efflux. These spikes increase the intestinal muscle tone but the BER itself rarely causes muscle contraction, and its function is to *coordinate peristaltic activity* (as evidenced by occurrence of these contractions only during its depolarizing parts).

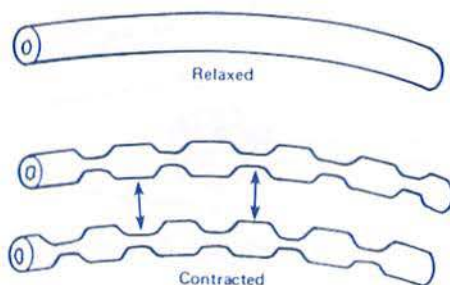


Figure 27 : Mixing (segmentation) movements in the small intestine.

Types of intestinal movements

In addition to the *tonic contractions* produced by the spike potentials described above, the following 2 types of movements occur in the small intestine :

(1) Mixing movements (segmentation contractions) : The circular muscle contracts at several sites, thus dividing a portion of the small intestine into nearly equal segments (each 2-3 cm long). A few seconds later, contractions appear in the middle of each segment while the previous constrictions disappear (figure 27), and such process is repeated at a rate that is determined by the frequency of the BER. Such contractions help food propulsion and move the chyme to and fro, which allows its mixing with the digestive juices and increases its exposure to the mucosal surface (thus promoting both digestion and absorption of food).

The segmentation contractions are *basically myogenic*, so they persist after section of the extrinsic nerves. They also persist after blocking the enteric nervous system (by local application of atropine or cocaine) but they become weaker.

(2) **Propulsive movements (peristalsis)** : After meals, these movements start at the duodenum, and are initiated by its distention as well as by the *gastro-enteric reflex* (distention of the stomach initiates peristalsis in the duodenum by impulses discharged through the myenteric plexus). However, they also occur in other parts of the small intestine, and they are *normally weak*. For this reason, the *movement of chyme in the small intestine is normally slow (average one cm / minute)* and thus, chyme normally passes from the pylorus to the ileocecal valve in 3-5 hours.

The peristaltic movements are *neurogenic* because they depend entirely on the integrity of the *enteric nervous system*. Stretch of the intestinal wall initiates a short (local enteric) reflex called the *myenteric reflex*. This reflex leads to ring constriction proximal to the area of stretch (figure 28) through neurons that liberate *acetylcholine and substance P* and relaxation of the muscle distal to it through *VIP releasing neurons*, and it results in a peristaltic wave that proceeds analwards.

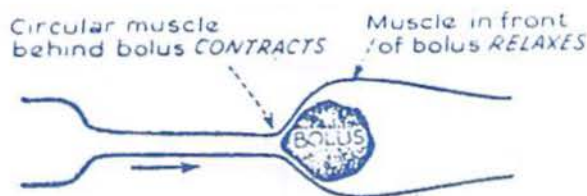


Figure 28 : Intestinal peristalsis.(the myenteric reflex).

Antiperistalsis and peristaltic rush

Most peristaltic waves pass analwards but *antiperistaltic movements may occur particularly during vomiting* (page 29). Strong peristaltic waves called *peristaltic rush or mass peristalsis* that spread rapidly over long distances in the small intestine are *not normally seen* but they occur *when the intestine is obstructed or its mucosa is irritated by infection* (partly due to vagal reflexes and partly through local enteric reflexes).

Control (regulation) of intestinal movements

(1) Nervous control

(a) **The intrinsic nerve plexuses** : These are *essential for peristalsis* and they also accentuate the segmentation contractions. After meals, peristalsis is stimulated by activity of these plexuses which occurs through the *myenteric and gastroenteric reflexes* (see above).

(b) **The extrinsic nerve supply** : This is *not required for both types of intestinal movements*. However, parasympathetic (vagal) stimulation increases the intestinal motility (particularly the peristaltic movement) while stimulation of the sympathetic nerves decreases it.

(2) Hormonal control

CCK, gastrin, motilin, insulin, serotonin and substance P increase the intestinal motility while secretin and glucagon decrease it.

The ileocecal valve and sphincter

The ileocecal valve is located where the ileum empties into the cecum (figure 29) and its function is to *prevent backflow of fecal contents from the cecum into the ileum*. The ileocecal sphincter is a thickened muscle at the last few centimeters of the ileum. Normally it is kept contracted and it relaxes only on arrival of strong intestinal peristaltic waves and when the stomach contracts to evacuate chyme (through a *gastroileal reflex* which is probably mediated by vagal impulses).

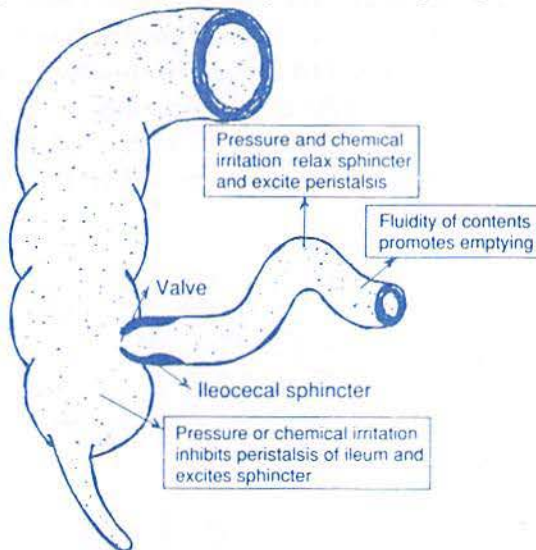


Figure 29 : The ileocecal valve and sphincter and the factors that affect chyme emptying into the cecum.

Feedback control of the ileocecal sphincter

An increase of pressure in the cecum (due to distention) or its irritation (e.g. in appendicitis) lead to *inhibition of ileal peristalsis and contraction of the ileocecal sphincter* (figure 29). Such *colonoileal reflex* is mediated through a local enteric reflex as well as a prevertebral ganglionic reflex, and it results in slowing of the rate of chyme emptying into the cecum.

Adynamic ileus (= paralytic ileus)

This is a condition of *marked decrease of intestinal motility that may occur after abdominal operations*. It occurs as a result of either (1) *Intestinal trauma* which inhibits the smooth muscle directly or through activation of the opioid receptors (2) *Peritoneal irritation* which causes reflex inhibition of the intestinal muscle through increased discharge of noradrenergic impulses along the sympathetic fibres in the splanchnic nerves.

CHAPTER 8

THE COLON (LARGE INTESTINE)

FUNCTIONAL ANATOMY

The structure of the human colon is shown in figure (30). From the functional point of view, it is divided into 3 parts :

(1) **Proximal colon** : This includes the cecum, ascending colon and proximal half of the transverse colon. Its function is mainly *absorption* (see below), so it is also called the *absorbing colon*.

(2) **Distal colon** : This includes the distal half of the transverse colon, the descending and sigmoid (pelvic) colon. Its function is mainly *storage of feces*, so it is also called the *storage colon*.

(3) **Rectum and anal canal** : The function of this part is *defecation*.

The diameter of the colon is much greater than that of the small intestine, and its length is *100- 110 cm in living adults*, but it elongates after death (becoming about 150 cm). The outer muscular fibres are collected into 3 longitudinal bands called *the teniae coli* which are shorter than the colon (so the wall of the colon normally forms outpouchings called *haustra or haustrations*).

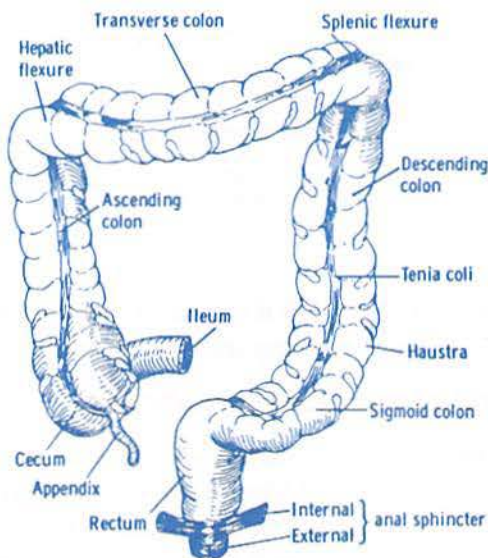


Figure 30 : The human colon (large intestine).

Mucosa of the large intestine

The mucosal epithelium in the large intestine is of the simple columnar type that contains many *goblet cells*. It contains simple tubular glands similar to the crypts of Lieberkuhn (but without villi), which together with the goblet cells *secrete mucus but no digestive enzymes*. Solitary *lymph follicles* are present specially in the cecum and appendix.

MUCUS SECRETION AND FUNCTIONS

Mucus secretion in the large intestine occurs in response to (a) *Mechanical and chemical excitation by the colonic contents* : This stimulates mucus secretion directly and through *local enteric reflexes*. (b) *Stimulation of the parasympathetic nerve supply to the colon* (the pelvic nerves): Mucus performs the following functions :

(1) **Protective function** : Mucus protects the mucosa from (a) Mechanical damage by the colonic contents (b) The effects of the pathogenic bacteria. Also, together with the alkaline secretion of the crypts (pH 8) which is caused by HCO_3^- , it provides a barrier that prevents acids formed by bacterial action from attacking the intestinal wall (see below).

(2) It exerts a **lubricant action** that facilitates the defecation process.

(3) It provides an **adherent medium** for holding fecal matter together.

FUNCTIONS OF THE LARGE INTESTINE

(1) **Absorption** : The colonic mucosa absorbs mainly Na^+ , Cl^- and *water*. Na^+ is actively absorbed and water follows passively along an osmotic gradient. The colon receives about 2 litres of *isotonic chyme* daily, most of the fluid in which is absorbed, leaving only about 250 ml of semisolid feces to be excreted (75 % of which is water and 25 % solids).

(2) **Secretion** : The colonic mucosa secretes (a) K^+ (b) HCO_3^- (c) Mucus (see above).

(3) **Digestion of cellulose** : This occurs *only in herbivorous animals* (grass-eating animals) because their large intestines contain beta-amylase enzymes (formed by bacteria) that can digest cellulose into glucose. In man, there are only alpha-amylases which cannot digest cellulose. However, cellulose in man is an important component of the *dietary fiber* (= all ingested food that reaches the large intestine in an unchanged state) which *adds bulk to the feces (thus helping defecation)*.

(4) **Excretion** : Certain heavy metals (e.g. bismuth and mercury) are excreted through the large intestine (in addition to the bile pigments).

(5) **Storage of feces** : This occurs specially in the *sigmoid colon* (which stores feces till the time of evacuation).

(6) **Defecation** : This is the process of feces evacuation (voiding out), and it is the function of the *rectum and anal canal* (see below).

(7) **Synthesis of vitamins** : The colon contains large numbers of bacteria (= *bacterial flora*). Some of these bacteria synthesize *vitamin K and several members of vitamin B* (specially folic acid) while others produce certain important *short-chain fatty acids*. These bacteria also participate in the *immune mechanisms* of the body (see below)

THE INTESTINAL BACTERIA

At birth, the colon is sterile but the bacterial flora becomes established early in life, and a great amount of bacteria passes in the stool (about **30 % of its total solids**). They are responsible for (a) *Colour of the stool* (by forming *stercobilinogen*) (b) *Acid reaction of the stool* (pH 5 - 7) because they form organic acids from carbohydrates (c) *Odour of the stool* because they form *indole and skatole* that have a characteristic odour.

EFFECTS OF INTESTINAL BACTERIA

There are 3 types of intestinal bacteria (1) **Pathogens**, which cause disease (2) **Symbionts**, which benefit the host and vice versa (3) **Commensals**, which have no particular effect on the host. These bacteria exert the following effects :

(A) Beneficial effects

(1) Synthesis of some vitamins (see above).

(2) Activation of the lymphoid tissue present in the intestinal wall to produce *immunoglobulins (antibodies)*, so germ-free animals often have hypoplastic lymphoid tissue and poorly-developed immune mechanisms.

(B) Harmful effects

(1) They are a source of disease both locally (enteritis) and generally (e.g. the overwhelming sepsis that may occur on exposure to radiation)..

(2) They form *ammonia*, which is normally *removed by the liver*, so in advanced liver disease, the ammonia level in the blood increases and leads to severe neurologic symptoms (= *hepatic encephalopathy*).

(3) They produce *cholesterol*, which produces harmful effects when its blood level exceeds a certain level.

(4) They *utilize (consume) ascorbic acid, vitamin B₁₂ and choline* (so giving animals small doses of antibiotics improves their growth rates because these substances will be preserved).

MOTILITY (MOVEMENTS) OF THE COLON

The movements of the colon are *generally sluggish* (which facilitates its absorption and storage functions). They are coordinated by a *basal electric rhythm (BER)*, the frequency of which increases gradually from about 2 / minute at the ileocecal valve to 6 / minute at the sigmoid colon. The colonic movements include the following :

(1) Mixing movements (segmentation contractions)

These occur mostly in the *proximal colon* and they are basically *myogenic*. They lead to formation of the bag-like sacs called *haustra* (or *hastrations*) and their repetition results in exposure of the chyme to the mucosal surface (which enhances absorption of water and electrolytes) and also slow propulsion of the colonic contents towards the rectum.

(2) Propulsive movements

These movements propel fecal matter toward the sigmoid colon, and they are 3 types :

(1) *Peristaltic waves* (as those occurring in the small intestine) : These occur *rarely* and *weak antiperistalsis is sometimes seen*.

(2) *The haustral contractions* (see above).

(3) *Mass action contractions (= mass movements)* : These occur only in the colon and are the *main propulsive movements*. They are contractions that involve segments of the colon, each is about 20 cm long and contracts as a unit. The colonic segments contract successively starting from the transverse colon, resulting in propulsion of the fecal matter towards the sigmoid. Such series of mass movements can be initiated by (a) Colonic irritation e.g. in ulcerative colitis (b) Overdistention of a colonic segment (c) Intense stimulation of the parasympathetic nervous system. However, they normally occur once (or a few times) each day, commonly *during the first hour after breakfast* as a result of either :

(1) *Gastrocolic and duodenocolic reflexes* : Distention of the stomach or duodenum leads to reflex mass movements in the colon. Such effect is most probably produced through *autonomic nerves*

(2) *Release of gastrin* : This hormone is released by the pyloric and duodenal mucosa on taking meals, and there is evidence that it *stimulates colonic movements*.

Transit time in the small intestine and colon

All of the undigested portion of a meal enter the colon after 8-9 hours. However, the *first part of the meal reaches the cecum in about 4 hours, the hepatic flexure in 6 hours, the splenic flexure in 9 hours and the pelvic colon in 12 hours*. After that, the transport is much slower, and 70 % of the residue is excreted within 72 hours while its total excretion requires more than a week.

DEFECATION

The anal sphincters

The anal opening (anus) is controlled by 2 *sphincters* (figure 31) that are *normally kept in a state of tonic contraction*. These are the *internal anal sphincter* (an involuntary smooth muscle) and the *external anal sphincter* (a voluntary striated muscle)..

Innervation of the rectum and anal sphincters

The rectum and internal anal sphincter are supplied by both parasympathetic and sympathetic nerve fibres, while the external anal sphincter is supplied by somatic nerve fibers from the pudendal nerves (figure 31).

(1) **Parasympathetic nerves** : These are the *pelvic nerves* (= *nervi erigentes*) which arise from the lateral horn cells in the 2nd, 3rd and 4th sacral segments of the spinal cord. Stimulation of these nerves leads to **defecation** by causing contraction of the rectal wall and relaxation of the internal anal sphincter. *Afferent fibres in these nerves transmit the sensation of rectal distention to the nervous system.*

(2) **Sympathetic nerves** : These are the *lesser splanchnic nerves* which arise from the lateral horn cells in the upper 3 lumbar segments of the spinal cord. Stimulation of these nerves **inhibits defecation** by causing relaxation of the rectal wall and contraction of the internal anal sphincter.

(3) **Pudendal nerves** (= skeletal motor nerve in figure 31) : These arise from *the anterior horn cells* in the 2nd, 3rd and 4th sacral segments of the spinal cord, proceed directly and supply the external anal sphincter.

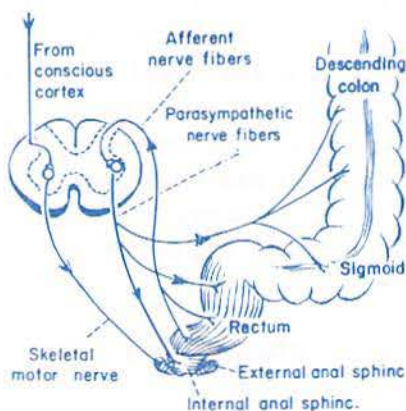


Figure 31 : Nervous control of defecation.

Mechanism of defecation (the defecation reflex)

Most of the time the rectum is empty of feces due to presence of a weak functional sphincter and a sharp angulation between the sigmoid colon and the rectum. However, when feces is forced into the rectum by the effect of the propulsive movements (see above), defecation is initiated *secondary to rectal distention*. The act of defecation occurs *primarily through a spinal parasympathetic reflex* which takes place as follows :

Rectal distention leads to discharge of impulses in afferent pelvic nerve fibres which stimulate the lateral horn cells in the 2nd, 3rd and 4th sacral segments of the spinal cord (*the defecation centre*). This centre in turn discharges impulses in efferent pelvic nerve fibres which cause contraction of the sigmoid colon and rectum, and relaxation of the internal anal sphincter. Such effects result in defecation if the external anal sphincter is relaxed, and can be fortified by straining (see below).

****** Rectal distention also initiates *an intrinsic reflex mediated by the local enteric nervous system* which causes the same effects produced by the spinal reflex. However, such reflex is normally *relatively weak to initiate defecation* (therefore, the spinal reflex is essential for the act)..

Voluntary control of defecation

In adults, rectal distention produces a sense of fullness and a desire to defecate by signals discharged to the sensory areas of the cerebral cortex along the ascending tracts of the spinal cord. The urge to defecate first appears when the rectal pressure increases to about 18 mmHg. However, defecation can be voluntarily inhibited (if the social conditions are not convenient) by increasing the tonic contraction of the external anal sphincter (although the tone of the internal sphincter is decreased). Such inhibition can be maintained as long as the rectal pressure is less than 55 mmHg but at more pressures, both anal sphincters are relaxed and expulsion of the rectal contents becomes urgent.

On the other hand, defecation can be voluntarily initiated at rectal pressures less than 55 mmHg if the social conditions are convenient through *straining*. This act involves taking a deep breath, closure of the glottis and contraction of the abdominal muscles. Such effects increase the intra-abdominal pressure which forces feces into the rectum. At the same time, the pelvic floor is lowered 1-3 cm and the *puborectalis muscle relaxes*, which reduces the angle between the anus and the rectum (*the anorectal angle*) from about 90° to 15° or less. These effects combined with relaxation of the external anal sphincter lead to defecation.

****** In infants, the spinal cord tracts are not myelinated. In this case, as well as in cases of spinal cord injuries in adults, the desire to defecate is lost and defecation occurs *automatically without voluntary control*.

CONSTIPATION

In normal persons, the frequency of defecation ranges from several times/day to once every 2-3 days. Constipation means slow movement of the feces through the large intestine. It is characterized by *prolongation of the intervals between defecations and excretion of dry hard stool*.

Causes of constipation

(1) Frequent voluntary inhibition of the defecation reflexes (*the commonest cause*). This leads to overstay of feces in the colon resulting in excessive water absorption (which renders it more dry and hard).

(2) Pathological obstruction of the large intestine e.g. by tumours and adhesions.

(3) Decreased motility of the colon as a result of either :

(a) Prolonged ingestion of diets that *leave little residue* (i.e. contain *little dietary fiber specially cellulose*), thus the bulk of feces becomes small and ineffective to initiate the defecation reflex.

(b) Old age, general weakness, lack of activity and debilitating diseases. These cases are associated with decreased colonic tone (= *atonic colon*) and weak defecation reflex.

(c) *Emotional stress* : These cases are associated with spasm of a colonic segment (= *spastic colon*) which results in decreased motility .

(d) *Hirschsprung's disease* (see below).

Effects (symptoms) of constipation

These include (1) Abdominal discomfort and distension (2) Nausea and anorexia (3) Headache. These symptoms are due to rectal distention and not due to absorption of toxic substances (because they are markedly relieved by evacuating the rectum and can be reproduced by distending it with an inert material).

Management (treatment) of constipation

- (1) Avoiding voluntary inhibition of the defecation reflex.
- (2) Ingestion of sufficient amounts of vegetables and fruits to add more dietary fiber and bulk to the stool by their cellulose content.
- (3) Improvement of health and performance of muscular exercise.
- (4) *Drugs* : An *enema* or one of the following drugs can be used :
 - (a) *Tranquilizers* (in cases of emotional stress or anxiety).
 - (b) *Laxatives* e.g. *paraffin* and *castor oils*.
 - (c) *Purgatives* e.g. *magnesium sulphate*.

DIARRHEA

This is an abnormal condition characterized by increased frequency of defecation associated with excretion of soft (or watery) stool.

Causes of diarrhea

Diarrhea occurs as a result of *hypermotility of the small intestine*, which is commonly due to either:

- (1) *Irritation of the intestinal mucosa by infections* (as occurs in cholera, enteritis and certain virus infections) or by certain toxic substances
- (2) *Nervous tension* (= *emotional or psychogenic diarrhea*) due to excessive stimulation of the parasympathetic nervous system.

Effects (symptoms) of diarrhea

Diarrhea is much more dangerous than constipation, and specially in infants, severe diarrhea may be fatal since it leads to :

- (1) Dehydration, hypovolemia and shock (due to excessive fluid loss).
- (2) Loss of electrolytes, particularly Na^+ and K^+ (loss of the latter may lead to hypokalemia).
- (3) Metabolic acidosis (due to excessive loss of HCO_3^-).

Management (treatment) of diarrhea

In addition to treatment of the cause, fluid and electrolyte loss can be reduced by oral administration of K^+ as well as Na^+ and glucose, so that Na^+ is absorbed via the Na^+ -glucose cotransporter (see chapter 10). Also bismuth subsalicylate is effective in reducing stool output.

Megacolon (Hirschsprung's disease)

This disease is due to *congenital absence of the ganglion cells in both intrinsic nerve plexuses at a segment of the distal colon*. The affected segment lacks peristalsis and becomes spasmodically contracted.

Endothelins are necessary for normal migration of certain neural cells and one cause of the disease in humans appears to be *a mutation in the endothelin B receptor gene*.

Feces passes through the affected segment with difficulty, resulting in *severe constipation* (and the patient may defecate once every 3 weeks). This allows large amounts of fecal matter to accumulate proximal to the affected segment leading to *marked distention of the colon* (its diameter may increase to 3-4 inches), so the condition is also called *aganglionic megacolon*.

However, in spite of the colonic enlargement and the severe constipation, there are usually *relatively mild symptoms for several months* (e.g. abdominal distension, anorexia and lassitude).

The condition can be treated *surgically* by resection (= removal) of the aganglionic segment, and the healthy portion of the colon above it is anastomosed to that below it (or to the rectum).

CHAPTER 9

THE GASTROINTESTINAL HORMONES

The gastrointestinal hormones are generally classified into the *gastrin and secretin families* in addition to other hormones (see page 6), and their actions were discussed in the corresponding chapters. In this chapter, these hormones will be considered in more detail.

(1) GASTRIN

Gastrin is a polypeptide hormone which exists in several forms (= *heterogeneity*) the commonest of which are *G17*, *G 34* and *G14* (which contain 17, 34 and 14 amino acids respectively in their molecules). *G 17* is the principal form with respect to gastric acid secretion and all gastrins are inactivated in the kidneys and small intestine.

Gastrin is secreted mainly by special cells called *G cells* present in the antral glands of the gastric mucosa.

Gastrin is also found in the *pancreatic islets in fetal life* (but not in normal adults), and gastrin secreting tumours called *gastrinomas* occur in the pancreas. It is also present in the anterior pituitary gland, hypothalamus and medulla oblongata as well as in some peripheral nerves (e.g. the sciatic and vagus nerves) but its function in all these sites is unknown.

Factors that control (regulate) gastrin secretion

(1) Factors that stimulate gastrin secretion

(a) *Luminal factors* : Gastric distention, presence of amino acids or peptides in the stomach, and when gastric acidity is decreased (page 24).

(b) *Nervous factors* : Vagal stimulation (however, the chemical transmitter released in this case is *not acetylcholine* but a special peptide called *gastrin-releasing polypeptide or GRP*).

(c) *Blood-borne factors* (e.g. calcium and epinephrine).

(2) Factors that inhibit gastrin secretion

(a) *Luminal factors* : Excess gastric acidity (at pH below 2) probably through release of *somatostatin* (which inhibits gastrin secretion).

(b) *Blood-borne* : Secretin, GIP, VIP, glucagon and calcitonin.

Actions of gastrin

The main physiological actions of gastrin are stimulation of gastric acid and pepsin secretion, stimulation of the growth of the gastric and intestinal mucosa (*trophic action*) and also probably stimulation of gastric motility.

****** In large doses, gastrin also causes (1) Contraction of the lower esophageal sphincter (2) Stimulation of insulin secretion (3) Stimulation of small and large intestinal motility (4) Relaxation of the ileocecal sphincter.

(2) CHOLECYSTOKININ (CCK)

This hormone is also called *cholecystokinin-pancreozymin (CCK-PZ)* because of its action on both the gall bladder and pancreas (see below). Like gastrin, it is a polypeptide which shows marked *heterogeneity* i.e. it exists in many forms (e.g. *CCK 58, 39, 33, 12 and 8*).

In the GIT, CCK is secreted by special cells called *I cells* in the mucosa of the duodenum and jejunum. It is also found in the brain (specially the cerebral cortex) and in the nerves that supply the distal ileum, colon and pancreas. It acts on **2 types of receptors** (CCK- A and CCK- B receptors), and little is known about its metabolism.

Factors that control (regulate) CCK secretion

CCK secretion is stimulated by contact of the digestive products to the intestinal mucosa (particularly peptides and amino acids) and also by fatty acids containing more than 10 carbon atoms. **A +ve feedback mechanism controls CCK secretion** as follows : The products of digestion—► CCK secretion—► flow of bile and pancreatic juice —► more products of digestion —► more CCK secretion. However, this vicious circle is terminated when the products of digestion move to the lower part of the GIT.

Actions of CCK

The physiological actions of CCK include (1) Contraction of the gallbladder wall (2) Trophic effect on the pancreas (stimulating its growth) and its stimulation to secrete a juice rich in enzymes (3) Potentiation of the action of secretin on the pancreas.

CCK also causes (a) Inhibition of gastric emptying (b) Enhancement of the motility of the small intestine and colon (c) Increase of secretion of the enterokinase enzyme (d) Stimulation of glucagon secretion from the pancreas (with gastrin) (e) Contraction of the pyloric sphincter (with secretin), thus preventing the reflux of duodenal contents into the stomach (f) In the brain, CCK may be involved in the regulation of food intake and may be related to the production of anxiety and analgesia.

(3) SECRETIN

Secretin is a polypeptide hormone that shows *no heterogeneity*. It is secreted by special cells called *S cells* that are located deep in the glands of the mucosa of the duodenum and upper jejunum.

Factors that control (regulate) secretin secretion

The secretion of secretin is stimulated by *acidity (HCl) and products of protein digestion*. Its release in response to acidity is subjected to a *negative feedback control* as follows : Secretin secreted in response to excessive duodenal acidity leads to increased secretion of alkaline juices (pancreatic juice and bile) which flow into the duodenum and neutralize the excess acid, thus inhibiting further secretion of the hormone.

Actions of secretin

The only physiological actions of secretin are (1) Stimulation of secretion of a *watery alkaline pancreatic juice rich in HCO_3^-* (which is secreted by the pancreatic duct cells via increasing cyclic AMP) (2) Increasing *HCO_3^- secretion by the duct cells of the biliary tract* leading to increase of bile flow (a *hydrocholeretic effect*, page 37).

Secretin also causes (a) Augmentation of the action of CCK on the pancreas (b) Inhibition of gastric activities, particularly acid secretion (c) Contraction of the pyloric sphincter (with CCK).

(4) GASTRIC INHIBITORY POLYPEPTIDE (GIP)

GIP is a polypeptide hormone that is secreted by *K cells* in the mucosa of the duodenum and jejunum. Its secretion is stimulated by glucose and fat in the duodenum. Its actions are the following :

(1) Inhibition of gastric secretion and motility. However, this effect is insignificant in normal rates of secretion of GIP, and many hormones produce the same effect but the most potent gastric inhibitory hormone is a polypeptide released from the jejunum called **peptide YY** (page 20).

(2) Stimulation of insulin secretion. It is the physiologic beta-cell stimulating hormone of the GIT, so it is called the *glucose-dependent insulinotropic polypeptide*. A glucagon derivative called **GLP-1** (glucagon-like polypeptide) also stimulates insulin secretion and is said to be more potent than GIP (so it may also be a second physiologic beta-cell stimulating hormone of the GIT).

(5) VASOACTIVE INTESTINAL PEPTIDE (VIP)

VIP is a polypeptide that is found mainly in nerves in the GIT as well as in the blood, the brain and many autonomic nerves (where it exists in the same neurons that contain acetylcholine). **Its actions are :**

(1) Stimulation of intestinal secretion rich in electrolytes and water (VIP-secreting tumours are often associated with severe diarrhea).

- (2) V.D. of peripheral blood vessels.
- (3) Inhibition of gastric acid secretion.
- (4) Relaxation of the intestinal muscle (including the sphincters).
- (5) Potentiation of the action of acetylcholine in the salivary glands.
- (6) Relaxation of the lower esophageal sphincter (page 15).

(6) MOTILIN

This is a polypeptide that is secreted by special cells (Mo cells) in the stomach, small intestine and colon. It causes *contraction of the gastric and intestinal smooth muscle*, and is a major regulator of gastrointestinal motility between meals (in the interdigestive state).

(7) SOMATOSTATIN

This is a polypeptide that exists in 2 forms (*somatostatin 14 and 28*). It was originally isolated from the hypothalamus (it is the *growth hormone-inhibiting hormone*), but it was found to be also secreted by the *D cells in the pancreatic islets and by similar D cells in the GIT mucosa*.

Its secretion is stimulated by gastric acidity, and is secreted in larger amounts into the gastric lumen than into the bloodstream. It is an *inhibitory hormone* that exerts the following actions :

- (1) Inhibition of secretion of gastrin, VIP, GIP, secretin and motilin.
- (2) Inhibition of gastric motility and secretion (and it may also mediate the inhibition of gastrin secretion produced by acid).
- (3) Inhibition of pancreatic exocrine secretion & gallbladder contraction.
- (4) Inhibition of absorption of glucose, amino acids and triglycerides.

OTHER GASTROINTESTINAL HORMONES

More than 15 types of hormone-secreting enteroendocrine cells have been identified in the mucosa of the GIT. In addition to the hormones mentioned above, these cells also secrete the following hormones :

(1) GLUCAGON

This is a polypeptide secreted by the *A cells in the mucosa of the stomach and duodenum*. It is similar to glucagon secreted by the A cells in the pancreatic islets. It is partly responsible for the hyperglycemia that may occur after pancreatectomy, but its *function in the GIT is unknown*.

(2) GLICENTIN

This is a polypeptide secreted by *L cells present in the mucosa of the lower part of the GIT*. It is formed in these cells from *glucagon precursors*, which also form *glucagon-like polypeptides 1 and 2 (GLP 1 and 2)*. As in case of glucagon, the *functions of all these substances in the GIT*

are *unknown*. Glicentin has some glucagon activity while GLP 1 is a potent stimulator for insulin secretion (see GIP, page 64). Both GLP 1 and 2 are also produced in the brain, in which GLP 2 acts as a neural mediator and inhibits food intake while the action of GLP 1 is unknown.

(3) GASTRIN RELEASING POLYPEPTIDE (GRP)

This is present in the vagal nerve endings that terminate on the G cells that secrete gastrin, and is the neurotransmitter that increases gastrin secretion from these cells on vagal stimulation. It may enter the circulation if secreted in large amounts and a part of its structure is almost identical to a hormone found in amphibia called *bombesin*.

(4) SUBSTANCE P

This is a polypeptide found in endocrine and nerve cells in the GIT. It may enter the circulation, and its main action is *increasing the motility of the small intestine*.

(5) NEUROTENSIN

This is a polypeptide produced by neurons and special cells in the *ileal mucosa* in response to fatty acids. It *inhibits GIT motility and increases the ileal blood flow*.

(6) PEPTIDE YY

This is a potent inhibitor to gastric secretion and motility (page 64) and it also inhibits food intake. It is released from the mucosa of the jejunum mainly in response to contact with fat.

(7) GHRELIN

This is a polypeptide secreted by the oxyntic cells of the stomach (page 16). It increases food intake & stimulates secretion of the growth hormone from the anterior pituitary gland, but its function in the GIT is unknown.

(8) GUANYLIN

This is polypeptide that is secreted by cells of the intestinal mucosa from the pylorus to the rectum. It binds to and stimulates guanylyl cyclase resulting in an increase of the intracellular cGMP content, and this increases the secretion of Cl^- (and fluids) into the intestinal lumen.

Guanylin receptors are also found in other tissues (e.g. the kidneys and liver), and guanylin may escape from the GIT and acts in an endocrine fashion to regulate fluid movement in these tissues.

****** Other gastrointestinal hormones that are now not believed to exist include *enterogastrone* (inhibits gastric activities and is probably GIP or peptide YY), *enterocrinin and duocrinin* (stimulate secretion of the intestinal juice) and *villikin* (induces movement of the intestinal villi).

CHAPTER 10

ABSORPTION IN THE GIT

All parts of the GIT are capable of absorption e.g. alcohol and water are absorbed from the gastric mucosa (page 26) and water and electrolytes are absorbed from the large intestinal mucosa (page 55). However, *the small intestine is the chief site of absorption because of the presence of the valvulae conniventes, villi and microvilli* (page 49).

In the small intestine, the mucosal cells (enterocytes) have brush borders that are lined by a layer rich in neutral and amino sugars called the *glycocalyx*. Next to the glycocalyx, there is an *unstirred layer*, and solutes must diffuse across this layer to reach the mucosal cells. The mucus that overlies these cells also constitutes a barrier to absorption.

Although absorption can occur by simple and facilitated diffusion, it is *primarily an active (vital) process as evidenced by the following* :

- (1) The intestinal O_2 consumption markedly increases during absorption.
- (2) If the temperature of an intestinal loop is raised, the rate of absorption in this loop markedly increases, and vice versa.
- (3) Occlusion of the blood supply to an intestinal loop markedly decreases the rate of absorption in this loop.
- (4) If serum is placed in the intestine, it will be completely absorbed although it has the same osmolality as the plasma.
- (5) The selective absorption of carbohydrates (e.g. galactose is absorbed faster than glucose although both have the same molecular weight).

Factors that affect intestinal absorption

- (1) **Vitality of the intestinal mucosa** : This depends on adequate blood flow and O_2 supply and certain vitamins specially vitamin B.
- (2) **State of digestion** : Proper digestion is essential for good absorption.
- (3) **Bile salts and lymph flow** : These are essential for fat absorption.
- (4) **Duration of contact of food to the intestinal mucosa** : If this is shortened (e.g. due to diarrhea), the rate of absorption will be reduced.
- (5) **The extent of the absorptive surface** : Pathological conditions (or surgical procedures) that reduce the intestinal surface by more than 50 % markedly decrease the rate of absorption.
- (6) **Intestinal mixing movements** : These help absorption by (a) Exposing the intestinal contents to the absorbing surface (b) Improving blood and lymph flow (c) Increasing the intra-intestinal pressure (see below).
- (7) **Movements of the villi** : These are 2 types, *side to side movement and pumping movement (shortening and elongation)*. They help absorption and are produced by branches of the *muscularis mucosae*. They are stimulated mainly by mechanical and chemical irritation of the villi. The hormone called villikin is not believed to exist (page 66).

(8) **Physico-chemical factors** : These include the following :

(a) **Concentration gradient** : The absorption of a certain substance by passive diffusion is favoured when its concentration in the intestinal lumen exceeds its concentration in the blood.

(b) **Intestinal osmolality** : The presence of hyperosmotic solutions in the intestine reduces the rate of absorption and vice versa.

(c) **Intra-intestinal pressure** : The higher this pressure, the greater will be the rate of intestinal absorption and vice versa (see above).

(d) **Solubility of the intestinal contents** : Increased solubility of a substance promotes its absorption e.g. acids help Ca^{2+} absorption, and bile salts help fat absorption by a hydrotropic action (page 39).

****** Normally, the small intestine receives about 9000 ml of fluid daily (2000 ml ingested and 7000 ml in the various digestive juices). About 8800 ml are absorbed in the small and large intestines while 200 ml are excreted in the stool.

Water absorption

Water absorption is a *passive process* (following absorption of electrolytes and nutrients by osmosis). Only a small amount of water moves across the gastric mucosa. However, in the small and large intestines, it moves in both directions across the intestinal mucosa *in response to osmotic gradients* until the osmotic pressure of the intestinal contents equals that of the plasma.

The osmolality of the duodenal contents may be hypertonic or hypotonic (depending on the ingested meal) but by *the time the meal enters the jejunum its osmolality becomes close to that of the plasma*.

Saline cathartics (purgatives) such as *magnesium sulphate* are poorly absorbed salts that retain water in the intestine by their osmotic effect, thus they increase the intestinal volume and exert a *laxative effect* (page 60)

Sodium (Na^+) absorption

Some Na^+ is absorbed passively in the small intestine depending on the concentration gradient (utilizing a *uniport carrier*). However, in the small and large intestines, Na^+ is absorbed mainly actively. In the small intestine Na^+ moves into the mucosal cells along its concentration and electrical gradients utilizing *symport carriers* (which cotransport Na^+ with other substances specially glucose) then it is actively pumped out at the basolateral borders of the mucous cells into the interstitial fluid by activity of the Na^+-K^+ ATPase (figure 32).

In the colon, Na^+ is also pumped out actively accompanied by passive absorption of water along an osmotic gradient.

****** Because Na^+ and glucose use the same carrier, they facilitate the absorption of each other (i.e. *their co-existence in the intestine increases the absorption of both*). This is the physiologic basis of treating acute loss of water and Na^+ in cases of severe diarrhea (e.g. in cholera) by oral administration of fluids that contain both NaCl and glucose (in most of these cases, the symport carrier of Na^+ and glucose is not affected).

Potassium (K^+) absorption

Normally, little K^+ absorption occurs actively in exchange for H^+ secretion (utilizing $\text{H}^+ - \text{K}^+$ ATPase) and ***K^+ is mostly transported into the intestinal lumen.*** Some K^+ is secreted with mucus but most K^+ moves passively down its electrochemical gradient into the intestinal lumen specially in the colon. That is why loss of the ileal and colonic fluids in cases of chronic diarrhea may lead to severe ***hypokalemia***. When the dietary K^+ intake is high, the secretion of aldosterone hormone is increased and more K^+ is secreted into the colon (by activating more $\text{Na}^+ - \text{K}^+$ ATPase pumps at the basolateral borders of the intestinal mucosal cells).

Chloride (Cl^-) absorption

Cl^- is absorbed in the small and large intestines mostly by ***passive diffusion following Na^+ absorption down an electrical gradient.*** On the other hand, Cl^- also normally enters the enterocytes from the interstitial fluid (utilizing $\text{Na}^+ - \text{K}^+ - \text{Cl}^-$ cotransporters in their basolateral borders) and is then secreted into the intestinal lumen via channels that are activated by cyclic AMP. The cholera vibrio produces a toxin that activates the adenylyl cyclase enzyme, leading to increased intracellular content of cyclic AMP. This increases Cl^- secretion and also inhibits the function of the Na^+ mucosal uniport carrier (so NaCl absorption is decreased). The accumulation of Na^+ and Cl^- in the intestinal lumen causes water retention by osmosis and leads to severe diarrhea (which is often rapidly fatal if not treated by administration of large amounts of solutions containing NaCl and K^+ as well as glucose).

ABSORPTION OF CARBOHYDRATES

Carbohydrates are absorbed mainly in the small intestine in the form of ***monosaccharides*** (and ***insulin has a little effect***) These sugars enter the blood capillaries in the villi, then they reach the liver via the portal vein.

Glucose absorption is Na^+ dependent, so a high Na^+ concentration increases while a low Na^+ concentration decreases glucose influx into the intestinal mucosal cells and similarly, Na^+ absorption is increased in presence of glucose (page 68). This is because both glucose and Na^+

utilize the same symport carrier called **SGLT 1** (= Na^+ dependent GLucose Transporter 1)

At the brush border of the mucosal cells, glucose moves inwards along with Na^+ where both are released. Na^+ is then pumped out of the cells into the lateral intercellular spaces by activity of Na^+-K^+ ATPase while glucose moves into the interstitial fluid mainly by **facilitated diffusion** (figure 32) utilizing a uniport carrier called **GLUT 2** (= GLucose Transporter 2). The energy for glucose transport is provided indirectly (by the active transport of Na^+ outside the cells). Therefore, the mechanism of glucose transport is a sort of **secondary active transport**, and the maximal rate of glucose absorption by this mechanism is about 120 gm / hour. The **glucose mechanism also transports galactose**.

Fructose is transported only by facilitated diffusion utilizing different carriers that are independent of Na^+ (and some is converted to glucose in the mucosal cells). It is transported from the intestinal lumen into the mucosal cells by GLUT 5 (not by SGLT 1) and out of these cells into the interstitial fluid by GLUT 2 (like glucose and galactose). On the other hand, pentoses, unlike hexoses, are absorbed by simple diffusion.

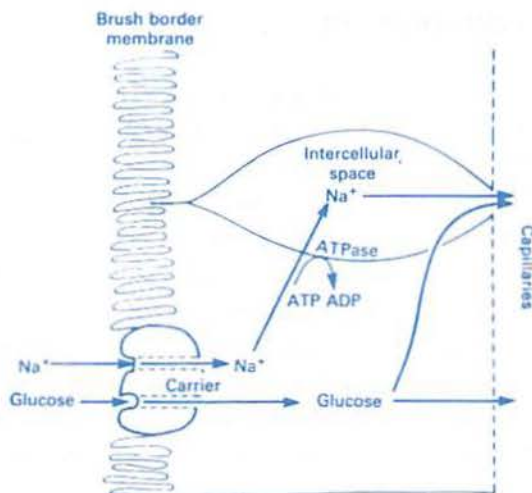


Figure 32 : Mechanism of glucose absorption in the small intestine.

ABSORPTION OF PROTEINS

Proteins are absorbed rapidly in the duodenum and jejunum (but slowly in the ileum) mainly in the form of **amino acids** (and some di and tri-peptides are also absorbed). The amino acids enter the blood capillaries in the villi, then they reach the liver via the portal vein. Normally, about 50 % of the digested protein comes from food, 25 % from proteins in the digestive juices and 25 % from desquamated mucosal cells. All proteins are digested

and absorbed in the small intestine except 2-5 % which are digested in the colon by bacterial action then absorbed. The protein in the stool is not of dietary origin but comes from bacteria and cellular debris.

7 different transport systems transport amino acids into the mucosal cells, 5 of which are Na^+ dependent (and 2 of the latter also require Cl^-). On the other hand, *di and tripeptides are transported by a system that requires H^+ instead of Na^+* . Congenital deficiency of the carrier responsible for transport of the neutral amino acids causes **Hartnup disease**, while congenital deficiency of the carrier responsible for transport of the basic amino acids causes **cystinuria**.

The transported amino acids plus those produced by intracellular hydrolysis of di and tripeptides accumulate in the mucosal cells then they enter the interstitial fluid by **facilitated diffusion** that requires 5 transport systems, 2 of them are Na^+ dependent.

In infants, moderate amounts of undigested protein are also absorbed (by **endocytosis** at the brush borders followed by **exocytosis** at the basolateral borders of the mucosal cells). In this way, the protein antibodies in the **maternal colostrum** (which produce passive immunity against many infections) can enter the infant's circulation undigested.

However, whole protein absorption declines with age (but adults still absorb small amounts). If a large amount of a foreign protein enters the circulation, it provokes formation of antibodies, and subsequent entry of the same protein results in an **antigen-antibody reaction** which may cause allergic symptoms (this explains the occurrence of allergic symptoms after eating certain foods).

Absorption of bacterial and viral protein antigens takes place in special cells (**microfold or M cells**) that overlie the lymphoid tissue in the intestinal wall. The M cells pass the antigen to the lymphoid tissue cells leading to activation of lymphocytes. These enter the bloodstream through which they return back to the intestinal mucosa, and on subsequent exposure to the same antigen, they secrete immunoglobulins (antibodies) that attack the antigen. Such **secretory immunity** is an important defence mechanism against invading harmful antigens.

ABSORPTION OF LIPIDS (FAT)

Fat absorption is greatest in the upper part of small intestine and 95 % of the ingested fat is normally absorbed. The bile salts and products of fat digestion (fatty acids and monoglycerides) form cylindrical aggregates called **micelles** (page 39). These micelles diffuse till reaching the unstirred layer (figure 33) where they move down their concentration gradient to the brush border of the mucosal cells. Here, lipids diffuse out of the micelles and enter the mucosal cells by **passive diffusion** (however, there is evidence that some carriers are involved).

Once fatty acids enter the mucosal cells, those containing less than 10-12 carbon atoms (short chain fatty acids) pass directly into the portal blood to the liver as free (= unesterified) fatty acids, while those containing more than 10-12 carbon atoms (long chain fatty acids) are **rapidly re-esterified** into triglycerides (also some of the absorbed cholesterol is esterified). In this way, the intracellular free fatty acid content is kept at a low level, which maintains a considerable **concentration gradient** for lipid diffusion from the gut lumen into the mucosal cells.

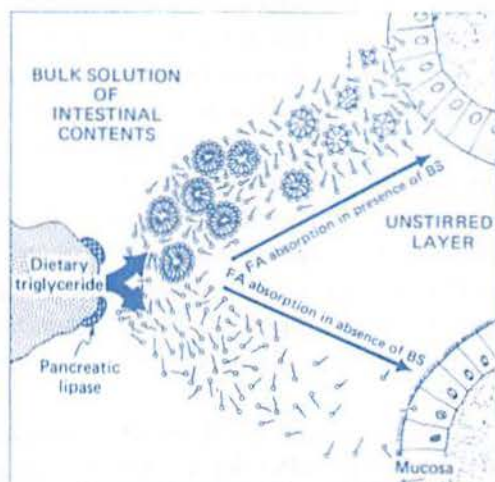


Figure 33 : Role of micelle formation in fat absorption. BS = Bile Salts.

In the Golgi complex, the triglycerides and cholesteryl esters are coated with a layer of protein, cholesterol and phospholipid resulting in formation of small particles called **chylomicrons** (figure 34). These are soluble in the cytoplasm, and when they approach the cell membranes they are extruded by **exocytosis** at the basal or lateral borders of the cells and enter the **lymph vessels in the villi** (= **the central lacteals**) where they accumulate (giving the lymph a **milky appearance**).

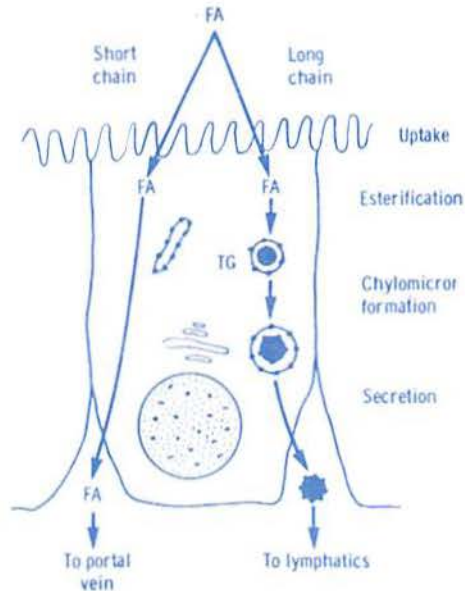


Figure 34 : Absorption of fat in the intestinal mucosal cells (notice chylomicron formation). FA = Fatty Acids. TG = Triglycerides.

****** In the mucosal cells, most of the triglycerides are re-synthesized from the absorbed fatty acids and monoglycerides. However, some triglycerides are formed from *glycerophosphate* (which is a product of glucose catabolism). The latter is also converted into *glycerophospholipids* that participate in chylomicron formation.

****** The processes involved in fat absorption are not fully acting at birth, so infants normally fail to absorb 10-15 % of the ingested fat.

****** Certain short-chain fatty acids (*SCFAs*) that contain 2-5 carbon atoms are *produced and absorbed in the colon*. They are formed by the action of bacteria on the complex carbohydrates and hard starches that escape digestion in the upper part of the GIT and enter the colon. These acids perform the following functions :

- (1) They exert a trophic effect on the colonic epithelial cells.
- (2) They are absorbed in exchange for H^+ , thus they help maintenance of the acid base balance.
- (3) They promote Na^+ absorption (but the mechanism of the *coupled Na^+ - SCFAs absorption* is unsettled).
- (4) They contribute in the total caloric intake.
- (5) They combat inflammation

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